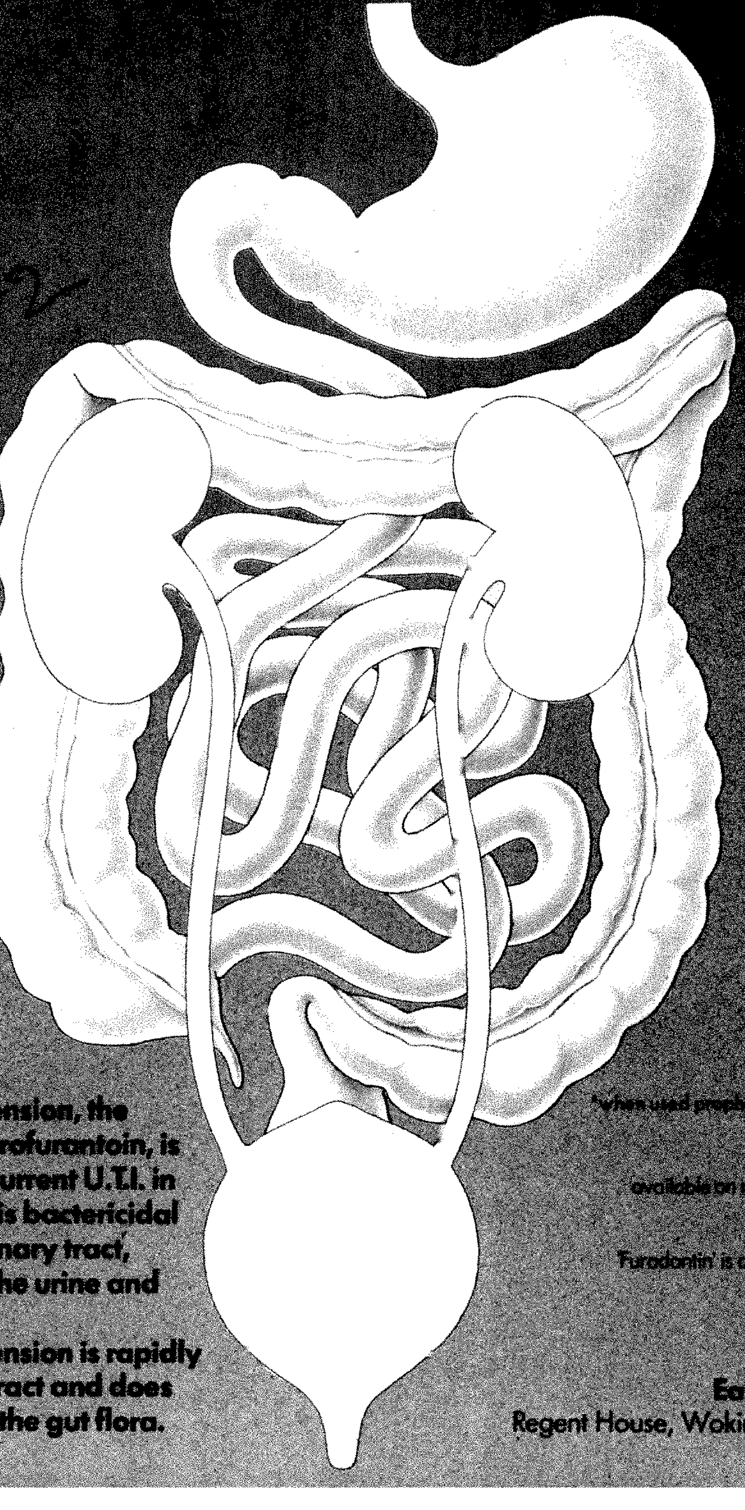
P25872

Furadantin Suspension

(nitrofurantoin)

To prevent lower urinary tract reinfection in childhood*



Furadantin Suspension, the only liquid form of nitrofurantoin, is ecommended for recurrent U.T.I. in childhood because it is bactericidal and specific to the urinary tract, being active in both the urine and he renal medulla.

Furadantin Suspension is rapidly absorbed in the G.I. tract and does not cause changes in the gut flora.

*when used prophylactically in susceptible individuals

Further information is available on request to the company.

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1. **Original articles** should, as far as possible, be arranged into the following main sections: 1. Summary; 2. Introduction; 3. Patients or Materials, Procedures or Methods; 4. Results; 5. Discussion and Conclusion.

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3. **Case reports.** Brief reports should not exceed 250 words, 2 illustrations and 3 references (approximately 1 page of the Journal). The sections should be: 1. Introduction; 2. Case Report; 3. Comment.

Papers must be submitted in Journal style. The text of articles should be typewritten in double-spacing on paper sheet size 21 × 29.7 cm (A4). There should be a minimum margin of 3 cm all round. Pages should be numbered with tables, legends and references typewritten on separate sheets. Authors should supply their qualifications, main appointment, and the name and address of the hospital or the laboratory on a separate page. In all full papers the literature should be summarised as concisely as is consistent with establishing the necessary basis for new material. Discussion and Conclusions should be strictly limited to the results presented. Repetition should be avoided. Summaries should be composed of very brief statements about each of the main sections. Only papers closely related to the author's work should be referred to; exhaustive lists should be avoided.

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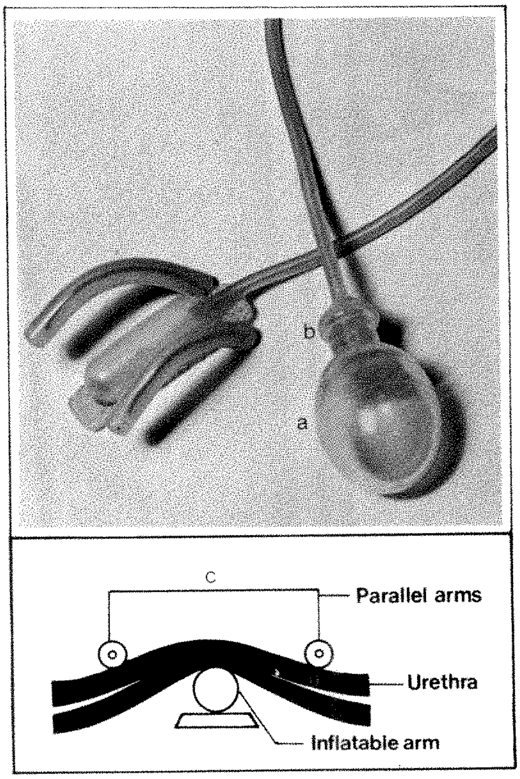

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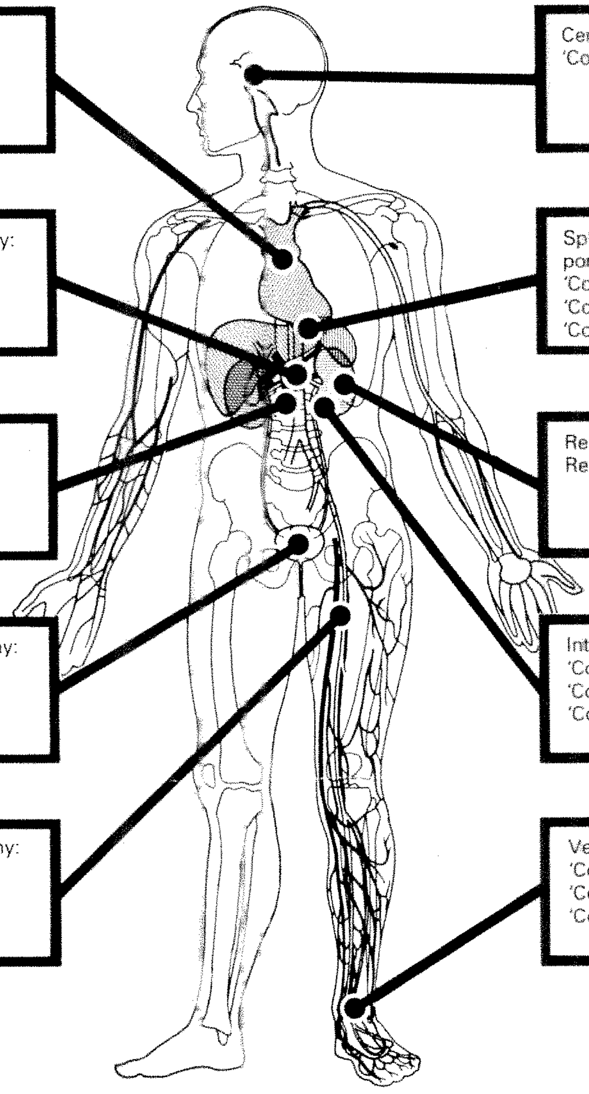

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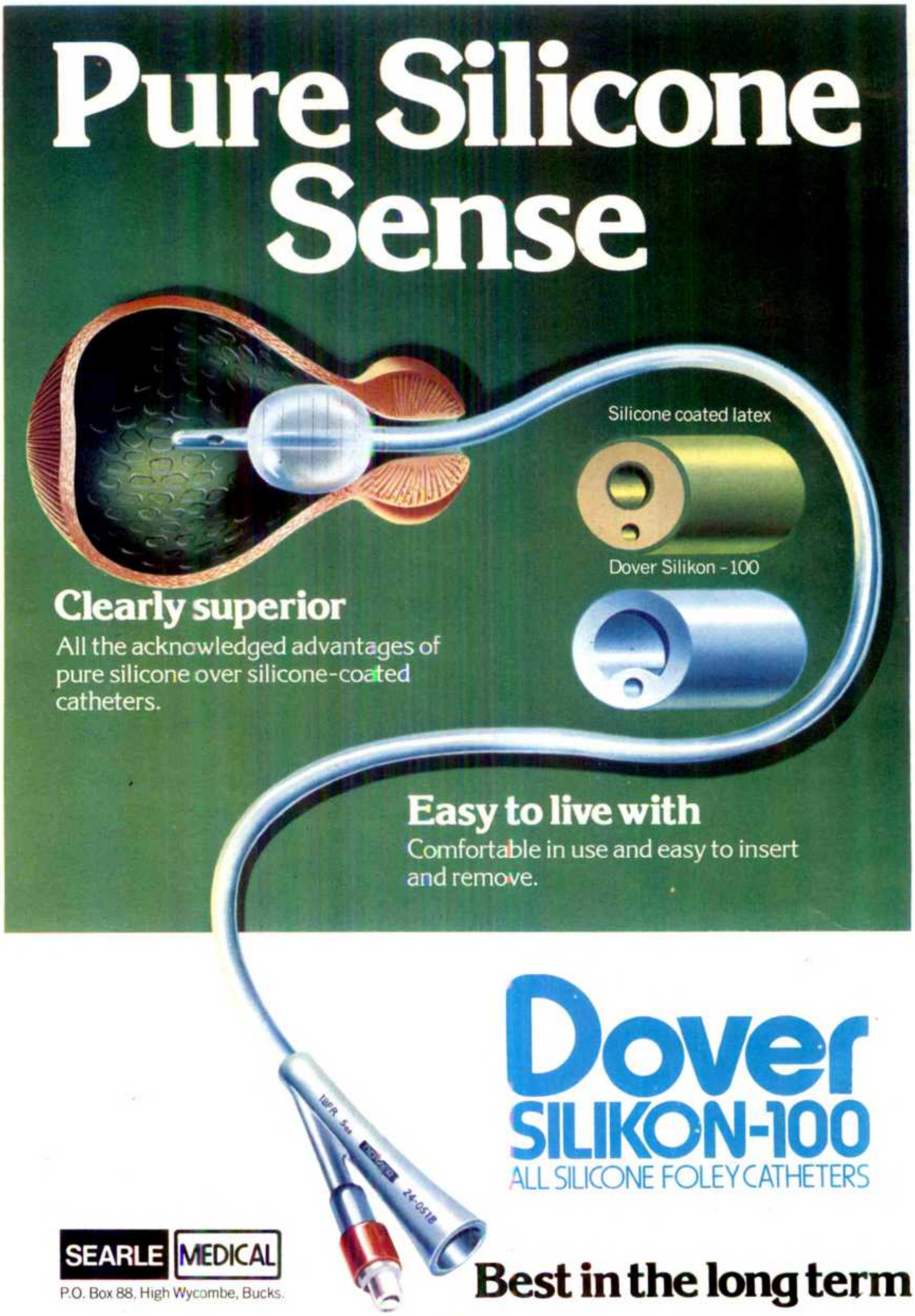

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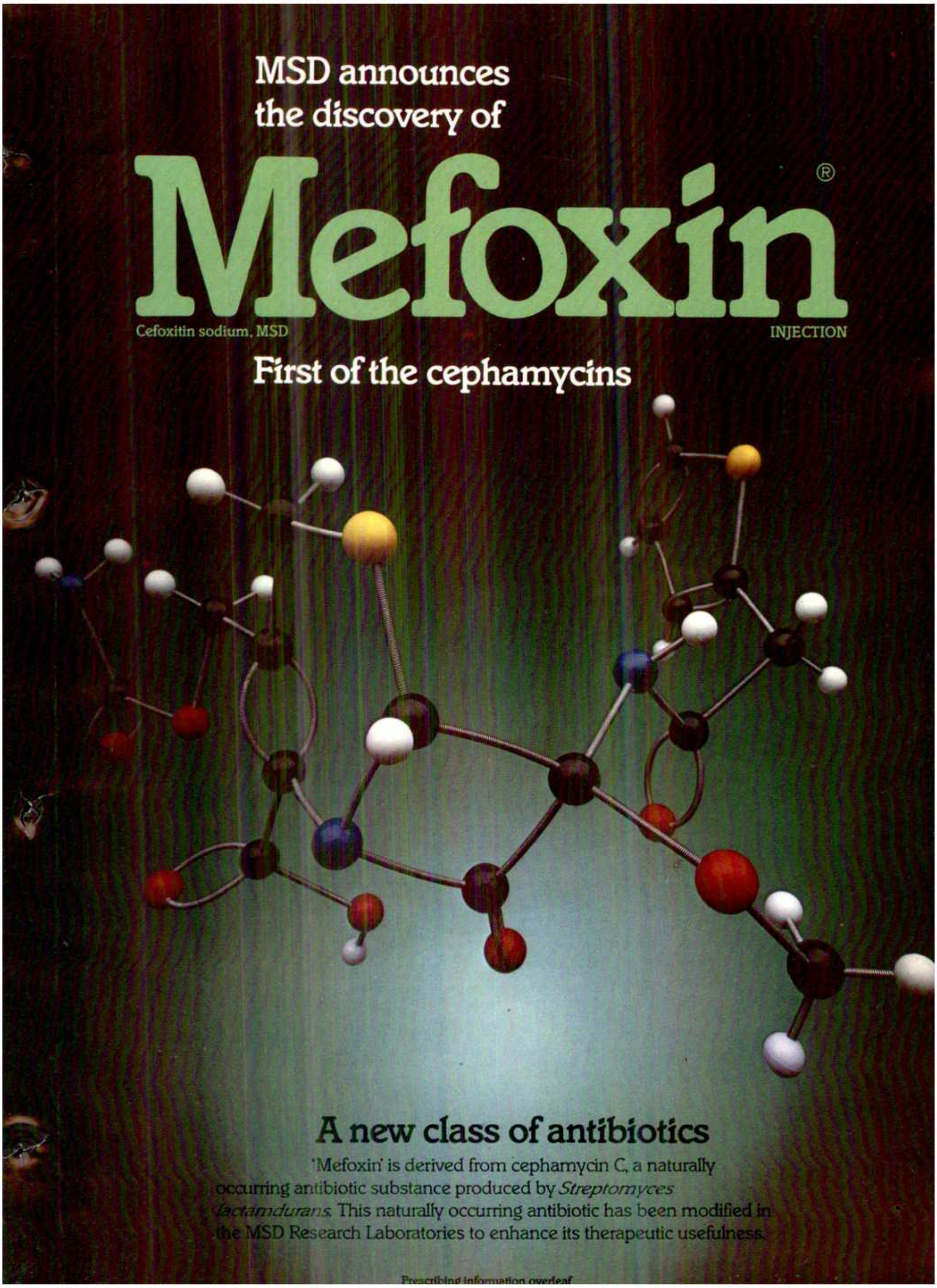


MSD announces
the discovery of

Mefoxin®

Cefoxitin sodium, MSD

INJECTION

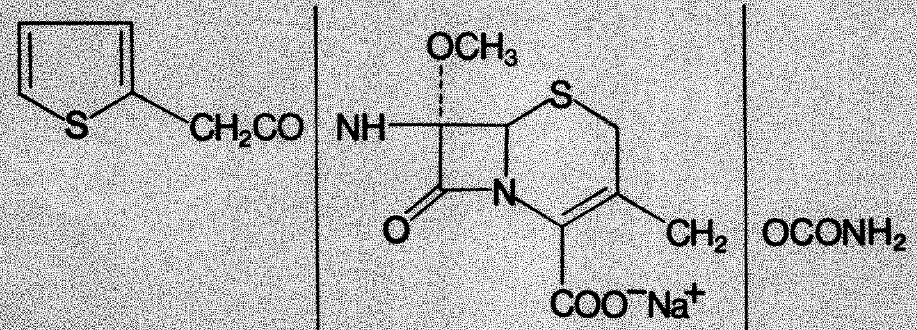
First of the cephamycins

A new class of antibiotics

'Mefoxin' is derived from cephamycin C, a naturally occurring antibiotic substance produced by *Streptomyces lactamdurans*. This naturally occurring antibiotic has been modified in the MSD Research Laboratories to enhance its therapeutic usefulness.

Prescribing information overleaf

'Mefoxin' has a unique molecular structure offering outstanding clinical benefits and a specific clinical profile.



Thienylacetyl side-chain:

enhances activity against Gram-positive pathogens

Cephamycin nucleus:

provides bactericidal activity against a wide range of pathogens, Gram-negative in particular. 7α-methoxy group protects against β-lactamase degradation

Carbamoyloxy side-chain:

protects antibiotic from being metabolised

▼Prescribing information

Indications

'Mefoxin' is a broad-spectrum bactericidal antibiotic indicated for the treatment of infections caused by susceptible strains of Gram-positive and Gram-negative pathogens both aerobic and anaerobic.

'Mefoxin' has been clinically effective not only in infections due to antibiotic-sensitive organisms, but also in infections due to organisms resistant to one or more of the following antibacterial agents: penicillin, ampicillin, carbenicillin, tetracyclines, erythromycin, chloramphenicol, cephalosporins, kanamycin, gentamicin, tobramycin, and sulphamethoxazole-trimethoprim.

Many Gram-negative pathogens are resistant to penicillins and cephalosporins through the action of the β-lactamases which are produced by these pathogens. 'Mefoxin' is remarkably stable in the presence of these bacterial β-lactamases, both penicillinases and cephalosporinases. Hence, the clinical efficacy of 'Mefoxin' extends to many infections caused by such pathogens.

'Mefoxin' is indicated for the treatment of the following infections caused by sensitive bacteria:
Peritonitis and other intra-abdominal and intrapelvic infections; female genital tract infections; septicaemia; urinary tract infections; respiratory tract infections; bone and joint infections; and skin and soft-tissue infections.

'Mefoxin' is indicated for adjunctive therapy in the surgical treatment of infections, including abscesses, infection complicating hollow visceral perforations, cutaneous infections, and infections of serous surfaces, whether caused by aerobes, mixed aerobes and anaerobes, or anaerobes.

Microbiology

'Mefoxin' is active *in vitro* against:

Aerobic bacteria

Gram-positive cocci including: Staphylococci: (including coagulase-positive, coagulase-negative, and penicillinase-producing strains); Group A beta-haemolytic streptococci *(Streptococcus pyogenes)*, Group B beta-haemolytic streptococci *(Streptococcus agalactiae)*, *Streptococcus pneumoniae (Diplococcus pneumoniae)*; other streptococci (except group D streptococci including enterococci, most strains of which are resistant, e.g. *Streptococcus faecalis*). *Gram-negative* cocci including *Neisseria gonorrhoeae* (including penicillinase-producing strains), *Neisseria meningitidis*. *Gram-negative rods (facultative anaerobes)* including *Escherichia coli*, *Klebsiella pneumoniae*, Klebsiella spp. *Proteus mirabilis*, *Proteus* (indole-positive) *Proteus vulgaris*, *Proteus rettgeri*, *Proteus morganii*, *Haemophilus influenzae*, *Serratia marcescens*; Providencia spp., Salmonella and Shigella spp.

Anaerobic bacteria

Gram-positive cocci including: Peptococcus spp.; Peptostreptococcus spp., Micro-aerophilic streptococcus. *Gram-positive rods including: Clostridium perfringens;* Clostridium spp., Eubacterium spp., *Propionibacterium acnes. Gram-negative cocci including:* Veillonella spp. *Gram-negative rods including Bacteroides fragilis*, *Bacteroides melaninogenicus*, Bacteroides spp (including both penicillin-susceptible and penicillin-resistant strains), Fusobacterium spp.

'Mefoxin' is active against some strains of the following bacteria: *Acinetobacter calcoaceticus* var *anitratum (Herellea vaginicola)*; *Acinetobacter calcoaceticus* var *lwoffi (Mima polymorpha)*; *Alcaligenes faecalis*, Citrobacter spp. and Flavo-bacterium spp.; Enterobacter spp.

'Mefoxin' is not active against Pseudomonas, most strains of enterococci and many strains of *Enterobacter cloacae*.

Dosage and administration

'Mefoxin' may be administered intravenously or intramuscularly (See reconstitution directions for each route below.) Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organisms, and condition of the patient.

Therapy may be started while awaiting the results of susceptibility testing.

Dosage: The usual adult dosage is 1 g or 2 g of 'Mefoxin' every eight hours. (See chart.)

In adults with renal insufficiency an initial loading dose of 1 g or 2 g may be given. After a loading dose, the following recommendations *for maintenance dosage* may be used as a guide.

Usual adult dosage

Type of infection	Dose	Frequency	Total daily dosage
Uncomplicated	1 g	Every 8 hours (occasionally every 6 hours)	3 g (4 g)
Moderately severe or severe	2 g	Every 8 hours (occasionally every 6 hours)	6 g (8 g)
Infections generally needing antibiotics in higher dosage	3 g (2 g)	Every 6 hours (Every 4 hours)	12 g

Maintenance dosage of 'Mefoxin' in adults with reduced renal function

Renal function	Creatinine clearance (ml/min)	Dose	Frequency
Mild impairment	50-30	1-2 g	Every 8-12 hours
Moderate impairment	29-10	1-2 g	Every 12-24 hours
Severe impairment	9-5	0·5-1 g	Every 12-24 hours
Essentially no function	<5	0·5-1 g	Every 24-48 hours

In the patients undergoing haemodialysis, the loading dose of 1 to 2 g should be given after each haemodialysis, and the maintenance dose should be given as indicated in the table above.

Intravenous administration: reconstitute 'Mefoxin' with Water for Injection BP. 1 g is soluble in 2 ml. Although 'Mefoxin' is very soluble, for intravenous use it is preferable to add 10 ml of Water for Injection BP to the 1 g vial or the 2 g vial. Shake to dissolve and then withdraw entire contents of vial into syringe.

For direct intravenous injection, 'Mefoxin' may be slowly injected into

Outstanding clinical benefits

Wide-ranging activity against Gram-negative and Gram-positive pathogens, anaerobes as well as aerobes.

Unusually high resistance to β-lactamase degradation.

Highly active against *Bacteroides fragilis* and strains of *E.coli*, Serratia, Klebsiella spp. and Proteus spp. (including indole positive strains) resistant to other antibacterial agents.

Offers high levels of active antibiotic in the body.

A record of relative safety comparable to the penicillins.

Prime indications include:

– Peritonitis, and other intra-abdominal and intrapelvic infections.
– Female genital tract infections
– Septicaemia
– Skin and soft tissue infections
– Bone and joint infections
– Urinary tract infections
– Respiratory tract infections (e.g. inhalation pneumonia)

Specific clinical profile

'Mefoxin' is exceptionally valuable wherever Gram-negative pathogens and anaerobes are involved in mixed infections. When mixed infections are suspected, therapy may be started while awaiting the results of susceptibility testing.

Mefoxin®

Cefoxitin sodium, MSD

INJECTION

First of the cephamycins

the vein over a period of 3 to 5 minutes or may be given through the tubing when the patient is receiving parenteral solutions.

An intermittent intravenous infusion of 'Mefoxin' may be employed when large amounts of fluid are to be given. However, during infusion of the solution containing 'Mefoxin', it may be advisable temporarily to discontinue administration of any other infusion solution at the same site (by using an appropriate IV infusion set).

A solution of 'Mefoxin' may also be given by continuous intravenous infusion (see below for compatibility and stability).

Intramuscular administration ONLY
Reconstitute 'Mefoxin' 1 g with 2 ml of Water for Injection BP, or 0.5% or 1% lignocaine hydrochloride (without adrenaline) solution. 'Mefoxin' is given by deep injection into a large muscle mass. Avoid injection into a blood vessel.

Compatibility and stability
A solution of 'Mefoxin' in Water for Injection BP may be added to the following solutions: 0.9% Sodium Chloride Injection BP, 5% or 10% Dextrose Injection BP, Dextrose and Sodium Chloride Injection (5%/0.9%, 5%/0.45%, or 4.3%/0.18%), Lactated Ringer's Injection USP, 5% Dextrose in Lactated Ringer's Injection, 5% or 10% invert sugar in water, 10% invert sugar in saline solution, 4.2% Sodium Bicarbonate Injection BP, M/6 Sodium Lactate Injection BP.

'Mefoxin', as constituted to 1 g/10 ml with Water for Injection BP, Water for Injection BP preserved with parabens or benzyl alcohol, 0.9% Sodium Chloride Injection BP, or 5% Dextrose Injection BP, maintains satisfactory potency for 24 hours at room temperature, for 96 hours under refrigeration, and for 13 weeks in the frozen state.

'Mefoxin' can be administered concomitantly with such antibiotics as gentamicin, tobramycin, carbenicillin or amikacin. When 'Mefoxin' is administered with another antibiotic, they should not be mixed in the same syringe.

Contra-indications
'Mefoxin' is contra-indicated in persons who have shown hypersensitivity to cefoxitin. In the absence of clinical experience, 'Mefoxin' should not be administered to patients who have shown hypersensitivity to cephalosporins.

Precautions
There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and other β-lactam antibiotics: penicillins, and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most β-lactam antibiotics.

Before therapy with 'Mefoxin', careful inquiry should be made concerning previous hypersensitivity reactions to β-lactam antibiotics. 'Mefoxin' should be given cautiously to penicillin-allergic patients.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. If an allergic reaction to 'Mefoxin' occurs, the drug should be discontinued.

The total daily dosage should be reduced when 'Mefoxin' is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see 'Dosage and administration') because high and prolonged serum antibiotic concentrations can occur from usual doses.

Interference with laboratory tests
A false-positive reaction to glucose in the urine may occur with reducing substances but not with the use of specific glucose oxidase methods.

Use in pregnancy
Use of the drug in women of childbearing potential requires that the anticipated benefits be weighed against possible hazards. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the foetus due to 'Mefoxin'. There are no controlled studies with 'Mefoxin' in pregnant women.

Nursing mothers
'Mefoxin' is excreted in human milk.

Infants and children
Pending the outcome of clinical trials in progress, the conditions for use of 'Mefoxin' in infants and children remain to be defined.

Side effects
'Mefoxin' is generally well tolerated. Side effects rarely require stopping treatment and usually have been mild and transient.

Local reactions
Thrombophlebitis has occurred with intravenous administration. Pain induration and tenderness after intramuscular injections have been reported.

Allergic
Maculopapular rash, urticaria, pruritus, eosinophilia, fever and other allergic reactions have been noted rarely.

Gastro-intestinal
Diarrhoea has been reported rarely.

Blood
Transient leucopenia and neutropenia have been reported. Some individuals, particularly those with azotaemia, may develop positive direct Coombs tests during therapy with 'Mefoxin'.

Liver function
Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase have been reported rarely.

Kidney
Elevations in serum creatinine and/or blood urea levels have been observed. The role of 'Mefoxin' in changes in renal function test is difficult to assess, since factors predisposing to pre-renal azotaemia or to impaired renal function usually have been present.

Presentation
In vials containing 1 g or 2 g of cefoxitin as the sodium salt. Each gram of cefoxitin contains approximately 51.5 mg (2.2 mEq) sodium.

Product licence numbers: 1 g, 0025/0130; 2 g, 0025/0131

Product authorisation numbers: 1 g, PA 35/42/1; 2 g, PA 35/42/2

Issued October 1978

Additional information is available to the medical profession on request.

Basic NHS cost is £4.47 for the 1 g vial, and £8.94 for the 2 g vial.

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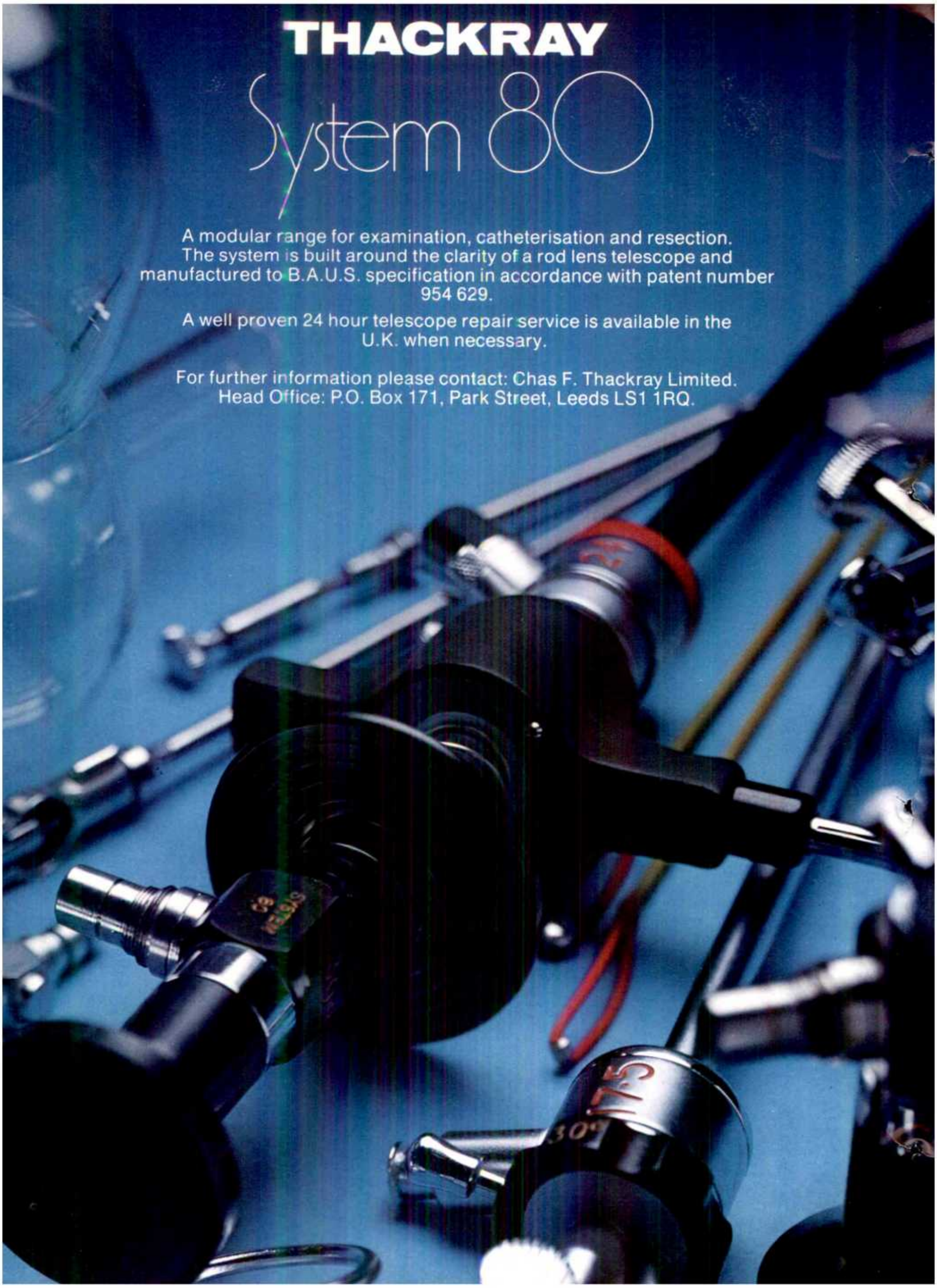

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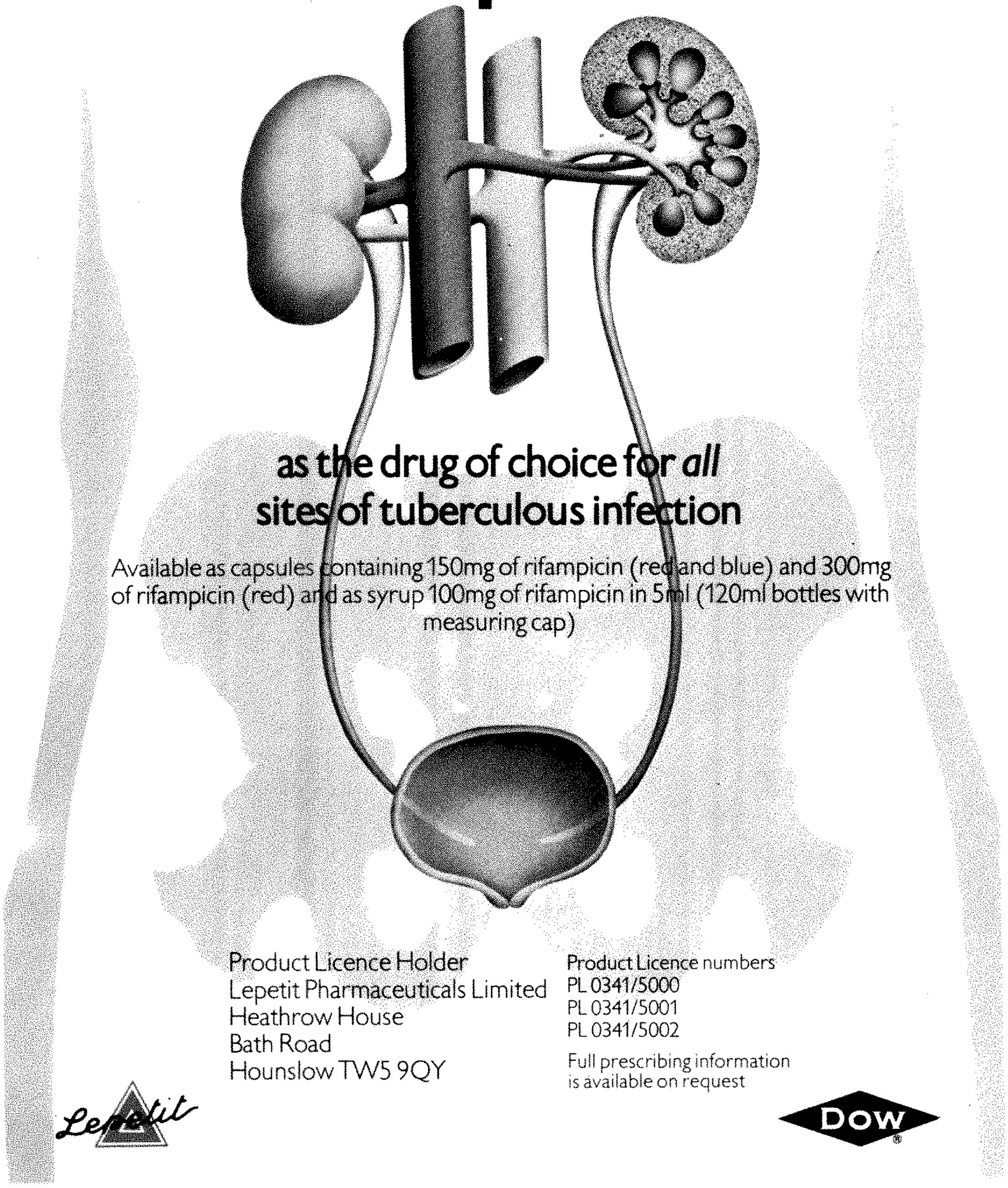

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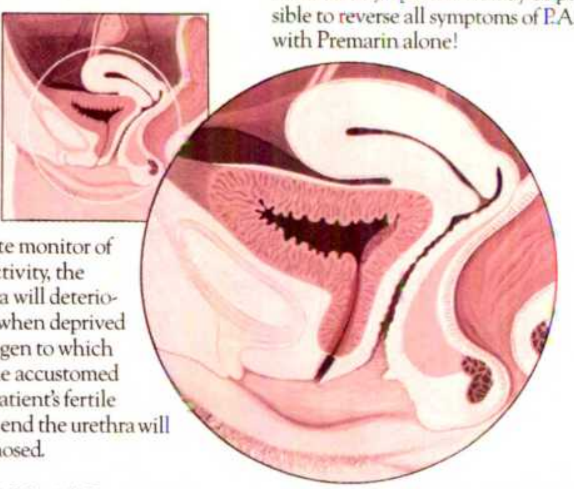
The Diagnosis and Treatment of P.A.U.

Post-menopausal Atrophic Urethritis

Older women presenting with frequency, urgency and painful micturition often describe their condition as 'cystitis'. There can hardly be a woman in existence who has not suffered the transient discomfort of a 'simple cystitis' at some time in her early life, but as she reaches middle age, although the symptoms may appear to her as the same, the cause, particularly in the absence of infection, may be atrophic changes in the distal urethra responding to hormonal disparities of the menopause.[1]

Untreated, these atrophic changes can be devastating and demoralising in their effect.[2]



A delicate monitor of oestrogen activity, the distal urethra will deteriorate rapidly when deprived of the oestrogen to which it has become accustomed during the patient's fertile years. In the end the urethra will become stenosed.

Treating P.A.U. with Premarin*

Treatment with Premarin 0.625mg tablets can effect a rapid and complete elimination of symptoms.[3]

1. Oestrogen deprivation can be confirmed by vaginal cytology or assumed in the presence of vaginal atrophy or dryness, or other symptoms of oestrogen lack.

2. Low-dose Premarin (0.625mg) administered cyclically – 21 days on, 7 days off – for 3 months. Urethral epithelium is remarkably sensitive to oestrogens and so will respond to this low dose.

3. Frank urinary tract infection should of course be treated with appropriate antibiotics or urinary anti-infectives.

4. If treatment is instigated in the early stages of this disorder – for instance within the first six/twelve months of symptoms – it may be possible to reverse all symptoms of P.A.U. with Premarin alone!

However in patients with a longer history of frequency and urgency, if oestrogen therapy does not effect a rapid and complete elimination of symptoms then the possibility of a secondary urethral stenosis should be considered.

References:

1. Willington, F. L. The Practitioner. 220, 739, 1978.
2. Smith, P. J. B., Ayerst Medical Library Vol. 2, No 2, 1978.
3. Smith, P. J. B., The Practitioner, 218, 97, 1977.

PREMARIN
(conjugated oestrogens)

Premarin tablets

Uses
Menopausal and post-menopausal oestrogen replacement therapy and allied disorders such as post-menopausal osteoporosis, atrophic vaginitis and post-menopausal atrophic urethritis.

Dosage and Administration
Menopausal and post-menopausal oestrogen deficiency: Premarin 0.625–1.25mg daily is the usual starting dose. Cyclic administration is recommended (three weeks' dosage followed by one week's rest). For maintenance, the lowest effective dose should be used. It is recommended that a physical examination, including endometrial assessment, whenever possible be performed at the time of the initial examination, and the endometrium assessed regularly thereafter at 6–12 month intervals. Break through bleeding is an indication for further investigation.

Contra-Indications: Uterine myomatosis. Endometriosis. Cancer of the breast and uterus. Active hepatic, renal and severe cardiac disease. Undiagnosed genital bleeding. Diabetes. Thyrotoxicosis. Pregnancy. Personal history of thrombosis.

Precautions
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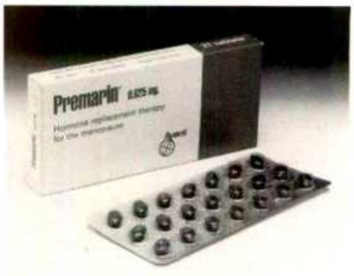

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4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

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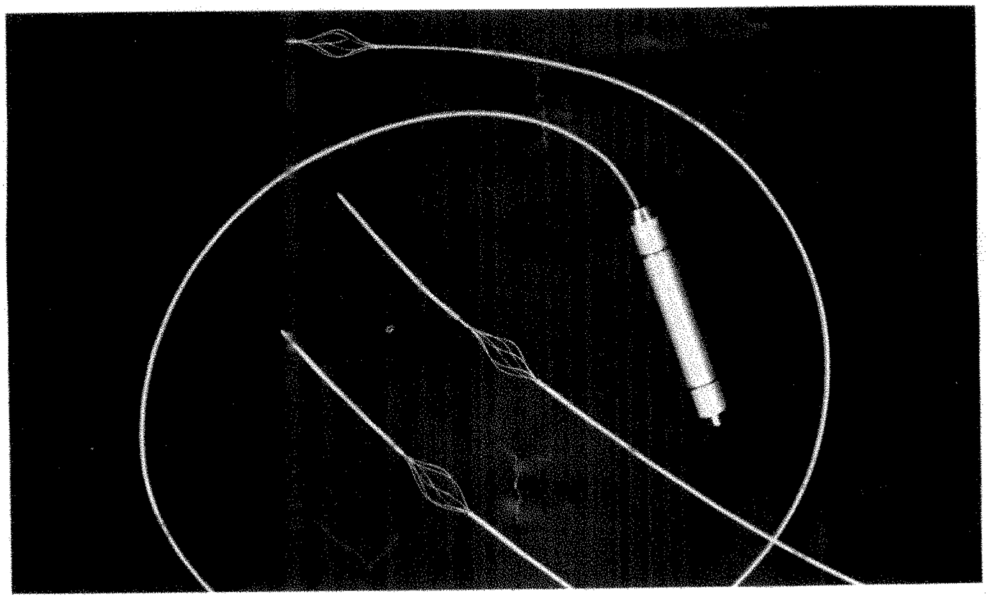

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Urinary Inhibitors of Calcium Phosphate Formation: the Inhibitory Activity of Normal and Artificial Urines

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Summary—Eleven urine samples from normal subjects inhibited the formation of calcium phosphate. In all cases the activity of the urine was identical with that of an artificial urine having the same concentration of urea, creatinine, sodium, potassium, magnesium, calcium, ammonia, sulphate, chloride, inorganic phosphate, citrate, isocitrate and pyrophosphate, and the same pH.

For many years it has been claimed that normal urine contains a potent unidentified substance which inhibits the formation of calcium phosphate. However, fractionation of urine using the techniques of ultrafiltration, precipitation, electrophoresis and paper chromatography failed to reveal the existence of any such substance (Sutor *et al.*, 1978). In order to establish that the inhibitory activity of urine can be explained in terms of the already known substances which affect the formation of calcium phosphate, the activity of normal urine samples was measured and compared with that of artificial urines having identical concentrations of relevant substances. These substances were deemed to be: (1) Calcium and inorganic phosphate which would accelerate the formation rate; (2) Citric acid and isocitric acid which form stable complexes with calcium and thus reduce the rate of the reaction; (3) Pyrophosphate which is adsorbed on to certain crystal faces and so prevents further deposition on them; (4) Sodium, potassium, ammonia, magnesium, sulphate and chloride, which are the main contributors to the ionic strength of the urine. Magnesium also inhibits the formation of calcium phosphate; (5) Urea and creatinine. These are 2 of the main constituents of urine and urea is thought to increase the solubility of calcium phosphate.

Materials and Methods

Analytical reagents, when available, and deionised water were used throughout.

Assay Method

The assay method chosen followed the formation of calcium phosphate at 25°C and it is described in detail elsewhere (Sutor and Percival, 1978b). Briefly, the method consisted of plotting the amount of sodium hydroxide required to keep the pH at 7.0 when calcium and phosphate ions were mixed so that their initial concentrations in the reaction beaker were 3 mmol/l. An amorphous phase was formed immediately which later changed to crystalline calcium phosphate. At each of these stages, sodium hydroxide had to be added to keep the pH constant. The time taken for the formation of the crystalline material was found to be highly reproducible both in water and in the presence of inhibitors. Furthermore, the reaction was slowed down by very small concentrations of substances which inhibited the nucleation of the amorphous phase as well as the crystal growth of calcium phosphate.

Material

The urines studied were early morning samples from 11 healthy adults with no history of urinary tract disease. The person was asked to empty his/her bladder before going to bed, and the sample was passed in the morning before breakfast. The age range of these normal subjects was 25 to 82 years and there were 4 females and 7 males.

No preservative was added in order to avoid any artefacts. Work began on the urine usually within 2 hours of voiding, and the necessary measurements were made within that day. Tests made on the urine showed that these measurements did not change during the day, nor did they appear to be affected by freezing the urine provided this did not cause precipitation.

On receipt, all urines were filtered through a No. 1 filter paper and then a Millipore filter (0.45 μm) and prefilter to remove any organic material which would act as a nidus in the crystal growth experiments. Crystals were not present. However, it was found that these early morning samples were usually very

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concentrated and often crystallised on standing at room temperature (21-23°C). After several experiments had to be abandoned because the urine precipitated during the day, it was found expedient to dilute it with water in the ratio of 3:1 (urine:water). This did not affect any of the measurements because diluted urine was used for most of them.

The pH of the urine and diluted urine was measured.

The activity of the urine was determined in the above assay system. The amount added was such that the formation of the crystalline material was delayed for about 15 to 20 min. This amount had to be determined by trial and error. Only 2 or 3 runs were made on each urine and these values were within ±3% of the mean.

Measurement of Urinary Constituents

Citric Acid This was measured by a modification of the method used by Welshman and McCambridge (1973) and that published in Biochemica Information (1975). As it was one of the first measurements made, the undiluted urine was used. The concentrations of the solutions were those recommended in Biochemica Information. Magnesium chloride was substituted throughout for zinc chloride, and the enzyme lactate dehydrogenase was omitted because it did not affect the results. The solution used for diluting citrate lyase consisted of triethanolamine (10 mmol/l), magnesium chloride (0.3 mmol/l) and ammonium sulphate (0.44 mol/l), and the pH was adjusted to 7.6.

To a cuvette (path length, 1 cm) was added 2.92 ml triethanolamine buffer (0.1 mol/l, pH = 7.6), 50 μl magnesium chloride (30 mmol/l), 100 μl urine, 25 μl nicotinamide adenine dinucleotide (NADH) solution (about 12 mmol/l), 10 μl malate dehydrogenase solution (2 mg/ml, Boehringer Corporation). After mixing, the absorbance at 340 nm was read in a Unicam SP 500 against a reference containing 100 μl of urine diluted with buffer to the same concentration as in the sample cuvette. Citrate lyase (30 μl of a solution containing 5 mg/ml, made by dissolving the lyophilised material in the enzyme diluting solution) was then added, and the absorbance was again read against the reference cuvette whose volume had been similarly adjusted. The concentration of citrate present in the urine was calculated from the difference between the 2 absorbance readings. Duplicate measurements were made on each sample and these were within ±2% of the mean value. Recovery of added citrate was excellent (99-100%), similar to that reported by Welshman and McCambridge (1973).

Table 1 Methods Used for the Determination of Electrolytes and Certain Compounds in Urine

Compound/ ion	*Method*	*Reference*
Sodium	AutoAnalyser: flame photometry	Technicon method N-21a
Potassium	AutoAnalyser: flame photometry	Technicon method N-21a
Calcium	AutoAnalyser: colorimetry	Halse (1967)
Magnesium	Atomic absorption	Hansen and Frier (1967)
Ammonia	Conway cells	Conway (1957)
Chloride	AutoAnalyser: colorimetry	Technicon method N-21a
Phosphate	AutoAnalyser: colorimetry	Technicon method N-4b
Sulphate	As barium sulphate	Folin (1905-6)
Creatinine	AutoAnalyser: colorimetry	Technicon method N-11b
Urea	AutoAnalyser: colorimetry	Technicon method N-1c

Only occasionally did the urine have a very high citrate concentration (>3.0 mmol/l) and then the amount added to the cuvette was reduced.

D-isocitric Acid D-isocitric acid was determined using the enzyme isocitrate dehydrogenase (Sutor and Percival, 1978a). Measurements were made on the neat urine and then on the diluted urine when urine was diluted to prevent precipitation occurring.

Pyrophosphate Pyrophosphate was measured using the enzyme uridine-5′-diphospho-glucose pyrophosphorylase (Sutor and Wilkie, 1978). Again measurements were made on the neat urine and then diluted urine when dilution was adopted.

Electrolytes, etc. The methods used for their estimation are given in Table 1.

Preparation of Artificial Urines

Artificial urines were prepared by pipetting out calculated volumes of standard stock solutions of sodium chloride, potassium chloride, sodium sulphate, magnesium sulphate and calcium chloride, and freshly prepared solutions of sodium citrate, sodium isocitrate, sodium pyrophosphate, urea, creatinine and ammonium chloride. (Because of the cost of D-isocitric acid, the stock solution contained DL-isocitric acid whose concentration was the same as that determined for D-isocitric acid.) A solution of sodium phosphate was prepared for each urine by dissolving calculated amounts of the acid and basic salts so that the pH of this solution was comparable with that of the original urine. The molarity of the stock solutions was about 20 times that of the molarity of the material in the original urine.

On mixing these solutions and diluting to a final volume of 100 ml, the concentration of each substance and ion, except chloride, was the same as in the original urine and, if necessary, the pH was adjusted to that of the urine. This adjustment was sometimes necessary because no account had been taken of the buffering action of citric acid when making up the phosphate buffer. Chloride was in slight excess to replace the

Table 2 Mean Concentrations and Range of Values for the Ions and Compounds Measured in the Early Morning Urine Samples from 11 Normal Subjects. Values Refer to the Original Undiluted Urines

Ion/compound	*Mean (mmol/l)*	*Range (mmol/l)*
Urea	274	147-434
Creatinine	10.3	4.1-18.0
Sodium	138	90-192
Potassium	33	20-71
Ammonia	25	10-37
Calcium	3.9	0.9-8.5
Magnesium	3.2	1.5-5.8
Chloride	114	35-247
Sulphate	16	8-31
Citrate	2.7	1.5-4.8
Isocitrate	0.31	0.10-0.53
Phosphate	22.5	7.9-45.8
Pyrophosphate	32.6*	8.5-88.0*

* Concentration in μmol/l.

organic acids present in urine whose concentrations had not been measured. The artificial urine was equivalent in concentration to either the neat or diluted urine, depending on which had been used for each person.

The artificial urine was tested in the assay system, and agreement between duplicate runs was very good, each value being within ±3% of the mean.

Measurement of Ionised Calcium

A check was made to see that the ionised calcium in the urine and corresponding artificial urine was the same, using the pH-independent dye, ammonium tetramethylmurexide (ATM). The maximum difference between the absorption spectra for free and bound ATM occurs at 480 and 550 nm (Varghese, 1973). Three ml urine and 100 μl saturated ATM solution were added to a cuvette. The solutions were mixed and the ratio of the absorbance at 480 and 550 nm was determined in a Unicam SP 500 against a reference cuvette containing 3 ml urine and 100 μl water. The agreement between this ratio for urine and its artificial urine was excellent for the first 4 urine samples investigated. (Individual values were within ±3% of the mean.) This measurement was then discontinued since it was apparent that all the major complexing agents of calcium had been accounted for.

Results

The mean concentrations and range of values observed for the different ions and compounds measured in the early morning urine samples are given in Table 2.

In the case of the 11 normal subjects tested, the inhibitory activity of the original and artificial urine was identical (Table 3).

Table 3 Time Taken for the Formation of Crystalline Calcium Phosphate in our Assay System. Mean Values for 2 or 3 Runs are Given for the Original and Artificial Urines for 11 Normal Subjects, and for the Reaction in Water Appropriate to each Run

Time (min) for reaction			*Volume (ml) of undiluted urine in test*
Water	*Urine*	*Artificial urine*	
10	34	35	4
9½	22	21½	3
9½	22	20	3
10	22	22	1
10	27	28	2
10	30	29	3
9	21½	21½	1.1
9	29	28	1.5
10	29	28½	2.6
10	30	26½	2.25
10	22	21½	1.5

Discussion

Our measurements have shown a wide range of values for some of the most important constituents in these early morning samples from normal subjects.

All the urine samples inhibited the formation of calcium phosphate, and the amount of activity could be accounted for in terms of substances which affect the solubility of calcium phosphate or inhibit the actual reaction. All these substances are well known constituents of urine and there was no unknown inhibitor, as many other workers have suggested.

It might be argued that different workers have used different assay systems and results obtained from each are not comparable. This is not the case. Provided information is given on the sensitivity of the method for detecting different types of substances which affect the formation of calcium phosphate, compounds which are detectable can be determined. From the data available, our assay method is either as sensitive as or more sensitive than other systems (Sutor and Percival, 1978b), and therefore substances detectable in these systems would be detectable in ours.

There was no contribution to the activity of the urine by the acid mucopolysaccharide, which is a potent inhibitor of the aggregation or crystal growth of calcium oxalate monohydrate (Robertson *et al.*, 1973). A comparison of the sensitivity of the 2 assay systems shows that an acid mucopolysaccharide as represented by heparin is not such an effective inhibitor of the crystal growth of calcium phosphate as of calcium oxalate, whereas the activity of pyrophosphate in the 2 systems is roughly comparable.

Our assay method, like most others, uses small concentrations of urine and so detects only the most potent substances affecting the formation of calcium phosphate. If it were feasible to use larger concentrations of urine, less potent substances, if present, should be detected. When urine was fractionated and concentrated extracts were tested, we ruled out the existence of such substances having a nominal molecular weight within the range 1000 to 10,000. It was also shown that any such substance with a molecular weight outside this range could not compare in potency with citric acid or pyrophosphate (Sutor *et al.* 1978).

After many years of pursuing an unknown inhibitor in urine, Howard (1976) also concluded that the "inhibitory potency" of urine in his ricketic cartilage assay system could be explained in terms of known constituents. He did not examine individual urine samples as we have done, but compared the activity of pooled normal urine samples with that of an average urine made from values given in standard textbooks. Pyrophosphate was not included in the average urine, but it was an essential constituent of most of our artificial urines. If it was omitted, the artificial urine usually showed less activity than the original urine. We do not, however, agree with Howard's statement that citric acid and phosphate react at physiological pH or at pH = 1 to form phosphocitric acid, which, he says, accounts for most of the activity in his system. Such a reaction is not chemically feasible, and acid conditions favour the hydrolysis of phosphate esters, not their formation. There are also many inconsistencies in the properties quoted for this substance. For example, phosphate esters are not hydrolysed by alkali, yet in the paper it was reported that taking the pH of urine to 12 destroyed the substance (phosphocitric acid) said to be formed at pH = 1. Moreover, with the sophisticated techniques of gas chromatography linked to mass spectrometry now available for identifying constituents of urine, phosphocitric acid has not been detected (Chalmers, personal communication).

Other workers who suggested that there were unidentified dialysable inhibitors in urine did not take into consideration all the substances and ions measured here. Fleisch (1965) found that the mean pyrophosphate content accounted for nearly half of the mean activity observed in a series of 28 urines. Citric acid, isocitric acid, magnesium and the ions contributing to the ionic strength were not taken into account, neither was the accelerating effect of the calcium and phosphate present in the original urines. Vermeulen *et al.* (1958) found more activity in urine than in the corresponding artificial urine. They omitted isocitric acid, pyrophosphate and ammonia from the latter.

Errors or artefacts in the assay system may also lead to false conclusions. For example, the latter workers did not control either the temperature of the assay, which is essential when quantitative studies are being made of crystal growth, or the pH which plays a vital role in calcium phosphate formation. In our assay method it was possible to introduce spurious activity by using inadequate electrodes (Sutor and Percival, 1978b). It is therefore suggested that assay methods should be rigorously tested for artefacts.

Acknowledgements

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British Journal of Urology (1979), **51**, 6-9

Oestrogen-Induced Renal Carcinoma

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Summary—Oestrogen may be implicated as an aetiological factor in the development of some renal carcinomas in man. The development of a renal carcinoma in 2 patients who had been treated with low-dose oestrogen for periods of 3 and 3½ years because of prostatic carcinoma is described. It is suggested that patients receiving prolonged oestrogen therapy should be evaluated for the presence of a renal carcinoma at regular intervals.

During the past 15 years there has been an increased interest in the concept of hormonal influence upon the development and progress of renal carcinoma. The administration of oestrogen-antagonists has become an established method of treatment in patients with advanced renal carcinoma. Bloom (1964) and other authors (Jenkin, 1967; Samuels *et al.*, 1968; Paine *et al.*, 1970) reported finding evidence of an objective improvement in from 7 to 20% of such patients treated with oestrogen-antagonists. This approach is based on the assumption that oestrogen may be implicated as an aetiological factor in the development of some renal carcinomas in man (Horning, 1956; Bloom, 1964). The question may therefore be asked as to whether prolonged oestrogen treatment in patients with carcinoma of the prostate might not be a contributory factor in the development of renal carcinoma in such patients.

One case of renal carcinoma in a man receiving long-term oestrogen therapy has been described by Bellet and Squitieri (1974). We describe 2 patients who had been treated for prostatic carcinoma with low-dose oestrogen for periods of 3 and 3½ years when renal carcinoma was discovered.

Case Reports

Case 1. A 65-year-old male was admitted to hospital because of disturbances in micturition, especially frequency and a poor urinary stream. Three and a half years previously he had undergone a transurethral resection of the prostate because of Stage C renal carcinoma. At that time intravenous pyelography had shown no pathological findings. Subsequently he had been receiving 3 mg diethylstilboestrol daily. The physical examination on his admission was unremarkable except for slight tenderness over the left loin and a small, firm, nodular prostate. Excretory urogram revealed a non-functioning left kidney. Renal scan showed very poor concentration over the left kidney and a normally concentrating and secreting right kidney. Cystoscopy was unremarkable. Left retrograde pyelography demonstrated a filling defect in the renal pelvis and a normal ureter (Fig. 1a). Bone scan disclosed a pathological concentration of radioisotope over D8-12. Chest X-ray was normal, as were the values of urea, creatinine and acid phosphatase.

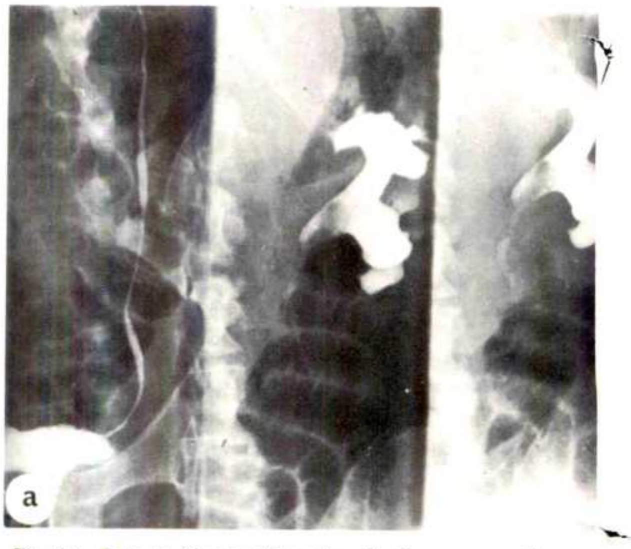

Fig. 1a Case 1: 65-year-old male with frequency and poor urinary stream. (a) Left retrograde pyelogram, demonstrating defect in renal pelvis and normal ureter.

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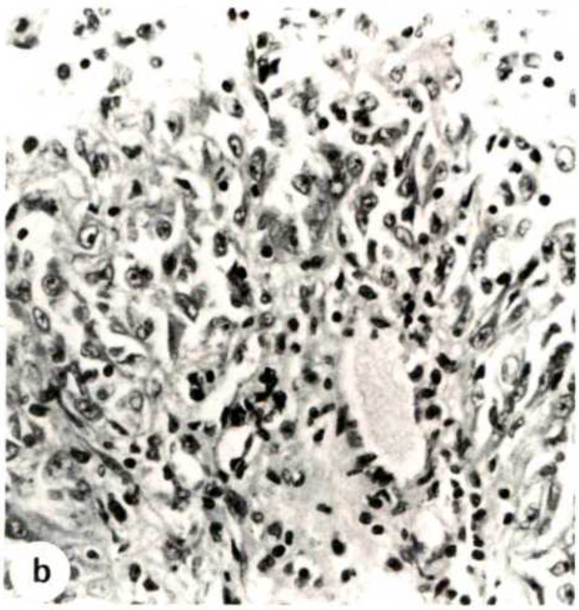
A left nephroureterectomy and bilateral orchiectomy as well as a needle biopsy of the prostate were performed. Histological examination revealed a renal carcinoma penetrating into the calices and renal pelvis. The tumour mass infiltrated the upper ureter and extended through the renal capsule into the perirenal tissue (Fig. 1b). The needle biopsy of the prostate revealed squamous metaplasia of the prostatic acini (Fig. 1c) with no evidence of carcinoma. The orchiectomy specimen disclosed metastatic prostatic carcinoma in the left spermatic vein (Fig. 1d).

The post-operative course was uneventful and within the following 3 months the patient gained 4 kg in weight.



Case 2. A 70-year-old male was transferred to our department from the orthopaedic ward, where he had been treated for a pathological fracture of the left femur. Histological examination of a specimen obtained from the fractured femur had revealed metastatic renal carcinoma (Fig. 2b) and excretory urography had demonstrated a space-occupying lesion in the left kidney. The patient had been receiving diethylstilboestrol, 3 mg daily, for the past 3 years after he had been diagnosed elsewhere as having carcinoma of the prostate solely on the basis of a rectal examination. Intravenous pyelography performed at the time when oestrogen treatment was started was reported to have been normal.

A renal arteriogram confirmed that the mass in the right kidney appear to be malignant (Fig. 2a). A bone scan revealed a pathological concentration in the left femur and a liver scan showed metastases in both lobes. Two transrectal biopsies of the prostate revealed no malignancy. The diethylstilboestrol was discontinued and treatment was instituted with medroxyprogesterone, 250 mg twice weekly.

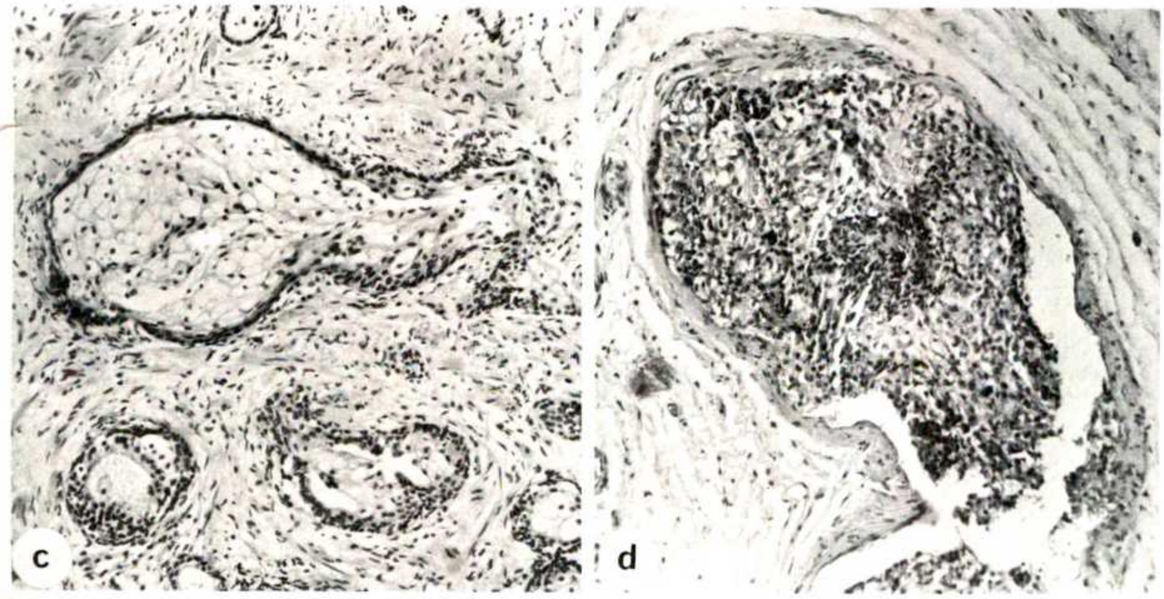


Fig. 1b-d Case 1: 65-year-old male with frequency and poor urinary stream. (b) (top) Histological appearance of the tumour of the kidney, demonstrating the presence of a papillary and tubular renal carcinoma (H & E × 500). (c) (left) Needle biopsy of the prostate, demonstrating squamous metaplasia of the prostatic acini (H & E × 500). (d) (right) Tumour embolus of prostatic carcinoma in left spermatic vein, showing low-grade differentiation of tumour cells (H & E × 200).

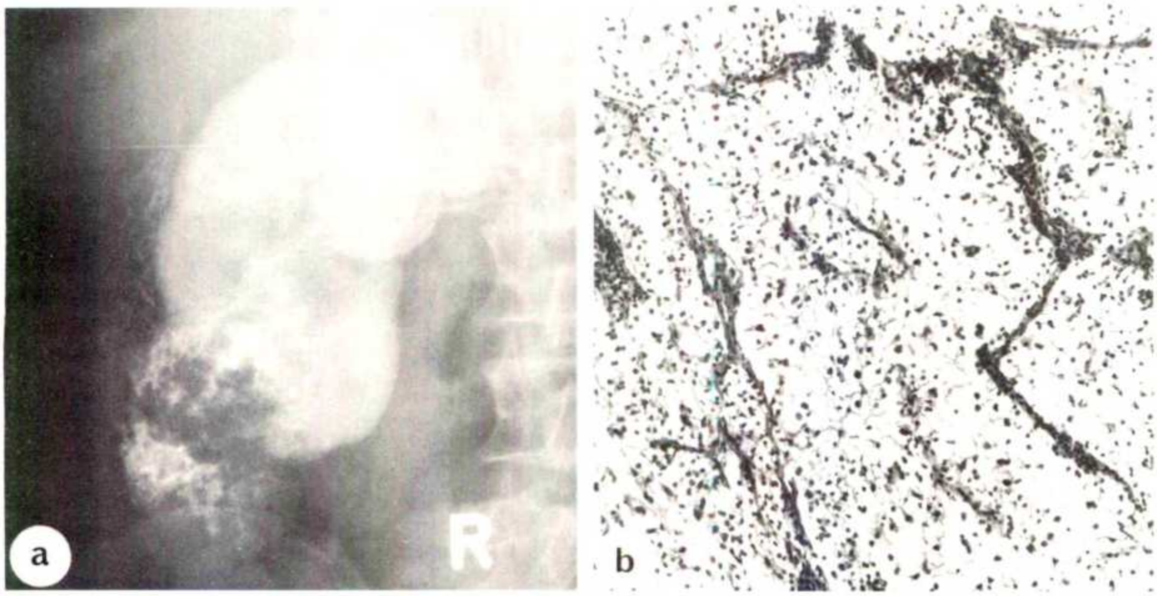


Fig. 2 Case 2: 70-year-old male with pathological fracture of femur. (a) Selective right renal arteriogram, demonstrating large vascular masses arising from the upper and lower poles of the kidney. (b) Histological appearance of femoral metastasis, showing clear cells arranged in solid alveoli, a finding characteristic of clear cell carcinoma of the kidney.

Discussion

Studies carried out in hamsters demonstrated that renal tumours may be induced by oestrogen and inhibited by oestrogen-antagonists (Horning, 1956; Bloom *et al.*, 1967). Epidemiological studies have shown that during the years commonly considered to be post-menopausal, renal carcinoma is 4 times more common in males than in females, whereas before this period the incidence of renal carcinoma is equal in both sexes. These findings led to the hypothesis that oestrogen or anti-androgens may be implicated as aetiological agents in the development of some renal carcinomas in man. This was further supported by the observation that anti-oestrogens have a cytotoxic effect on tissue cultures of human renal carcinoma (Tchao *et al.*, 1968) as well as by the objective remission seen in males with metastatic renal carcinoma who were treated with anti-oestrogens (Jenkin, 1967; Samuels *et al.*, 1968; Paine *et al.*, 1970; Bloom, 1973).

Since carcinoma of the prostate is one of the most frequent tumours found in males, and assuming that there is a probable association between oestrogen and the development of renal carcinoma, one might expect to find a significant number of renal tumours among patients with prostatic carcinoma who are being treated with oestrogen. However, the literature appears to contain only a single report of such a case, in which renal carcinoma was found after 7 years of therapy with low-dose oestrogen (Bellet and Squitieri, 1974). Since only 7 to 20% of renal carcinomas show an objective improvement following anti-oestrogen therapy, *i.e.* are sex hormone dependent, only a relatively small percentage of patients receiving oestrogen therapy constitutes a high risk group. It is also probable that only prolonged administration of oestrogens will serve to induce development of the tumour, although the effect of this drug may be manifest much more rapidly upon an already existing but possibly undiagnosed renal carcinoma, with subsequent fulminant growth of the tumour if it is indeed hormone dependent. In cases where a tumour is discovered, alternative forms of treatment should be used to replace the oestrogens.

In both our cases distant metastases were found, in one to the thoracic vertebrae and in the other to the liver and the left femur, where they caused a pathological fracture. In the first patient a bilateral orchiectomy was performed but in the second patient repeated biopsies showed no malignancy in the prostate. In both, oestrogen treatment was stopped and in the second patient treatment with medroxyprogesterone was instituted.

It is concluded that patients with carcinoma of the prostate receiving prolonged oestrogen therapy should undergo intravenous pyelography at regular intervals even though there is no clinical or laboratory evidence for the presence of a tumour in the kidney.

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Diuresis Renography and Morphology in Upper Urinary Tract Obstruction

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Summary—The results of a combined study of 25 patients with idiopathic hydronephrosis are presented. Diuresis renography was performed pre-operatively and surgically removed specimens of the renal pelvis and ureter were examined by light and electron microscopy. There was good correlation between the results of these 2 methods of assessment which have defined 2 broad categories of patients with renal pelvic dilatation. These findings are discussed with particular reference to the clinical value of diuresis renography.

Diuresis renography has recently been introduced as a method of evaluating upper urinary tract dilatation found on intravenous urography (O'Reilly *et al.*, 1978). It is a simple, rapid, non-evasive test which has enabled 2 different categories of patients with suspected pelviureteric junction obstruction to be defined.

It has recently been shown that characteristic morphological changes, as determined by light and electron microscopy, occur in the renal pelvic wall of cases of established pelviureteric junction obstruction (Gosling and Dixon, 1978).

In the present study, the results of diuresis renography in a series of patients with idiopathic hydronephrosis have been compared with morphological features of the renal pelvis and ureter. This study has been undertaken to ascertain whether there is a consistent relationship between the excretion pattern on the functional diuresis renogram and the structural features of the upper urinary tract.

Patients and Methods

Twenty-five patients were examined and provided 26 specimens. The age range was 9–57 years (mean 33 years). All cases studied had dilatation of the renal pelvis found on intravenous urography and were judged on clinical grounds to require surgery. The operations performed are shown in Table 1. Each of these patients with suspected pelviureteric junction obstruction had either an Anderson-Hynes pyeloplasty or a nephrectomy.

Table 1 Idiopathic Hydronephrosis—Operations Performed

First Operation—21 Specimens	
Anderson-Hynes Pyeloplasty	20
Nephrectomy	1
Repeat Operation—5 Specimens	
Anderson-Hynes Pyeloplasty	3
Nephrectomy	2

Probe renography was performed in all patients, both with and without a diuretic stimulus. No special preparation was required for this test but a normal state of hydration was ensured. A standard renogram was carried out initially using an intravenous injection of Iodine 131 labelled Hippuran in a dose of 0.4 μCi/kg body weight. This was followed by an oral fluid load and a second renogram 3 min after an intravenous injection of the diuretic Frusemide. In cases where there was no excretion of the isotope from the affected kidney approximately 20 min after the start of the initial renogram, the diuretic was given at this stage and the response observed while the tracing continued uninterrupted. On the basis of the examination of the standard and diuresis renograms patients with suspected upper tract obstruction were divided into 4 groups as follows: (Figs. 1–4)

I. Both the standard and diuresis renograms were normal.
II. Both renograms had an obstructive pattern.

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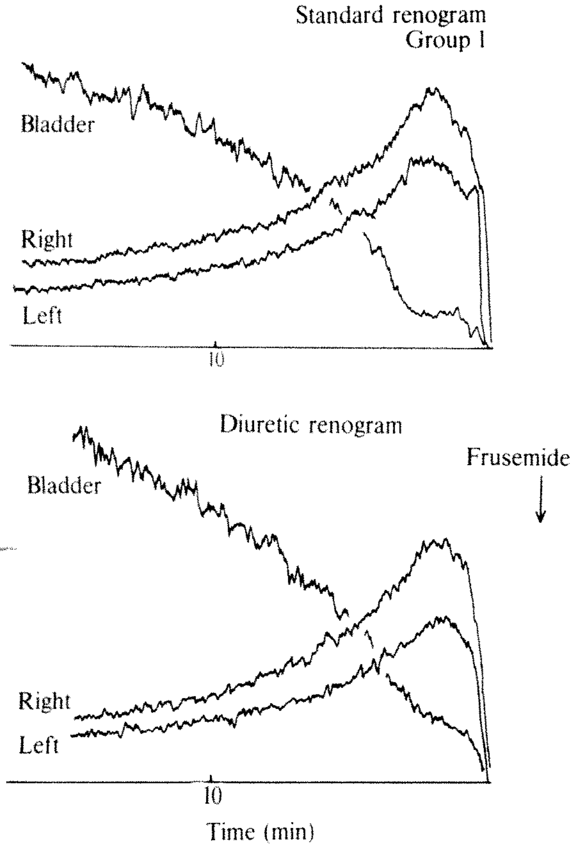

Fig. 1 Group I response showing standard and diuresis renograms.

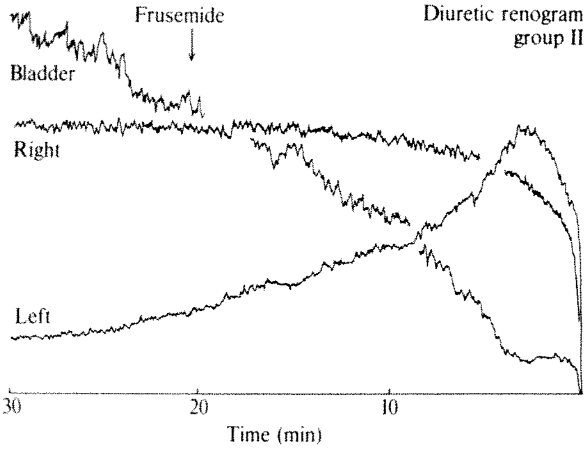

Fig. 2 Group II response showing an obstructive pattern on the right side with no improvement in excretion after Frusemide.

IIIa. The initial renogram tracing was obstructive but rapid isotope elimination occurred after diuresis.

IIIb. Standard renography showed an obstructive pattern and diuresis produced only a slight improvement in excretion.

Three patients in whom renography showed impairment of function in the presence of suspected upper urinary tract obstruction have also been included in this series. It has been assumed that the diminution in renal function in these cases was due to obstruction (*vide infra*).

The surgically removed specimens were received fresh from the operation. Representative tissue samples were taken from all parts of the specimen, including sites as proximal as the minor caliceal/parenchymal junction in the nephrectomy material. The tissue was prepared for light and electron microscopy using the methods described in a recent report (Gosling and Dixon, 1978), Control tissue was obtained from the upper urinary tract of a nephrectomy specimen removed for causes other than obstruction or infection.

Results

The results of diuresis renography in this series of patients and their relationship with the morphological observations are shown in Table 2. An obstructive pattern was obtained in 8 cases by a group II response and 9 cases by a group IIIb response. Three kidneys were found to be poorly functioning and 2 renogram patterns were equivocal. In all of these cases characteristic morphological abnormalities were demonstrated in the renal pelvis. These morphological changes included excessive amounts of collagen and elastic fibres between and within the muscle bundles, separating individual muscle cells from one another (Fig. 5). Fine structural changes in the smooth muscle cells observed by electron micro-

Table 2 Idiopathic Hydronephrosis—Results

Diuresis Renography Response		*Morphology*
II	8	Abnormal
IIIb	9	
Poor function	3	
Equivocal	2	
I	1	Normal
IIIa	3	

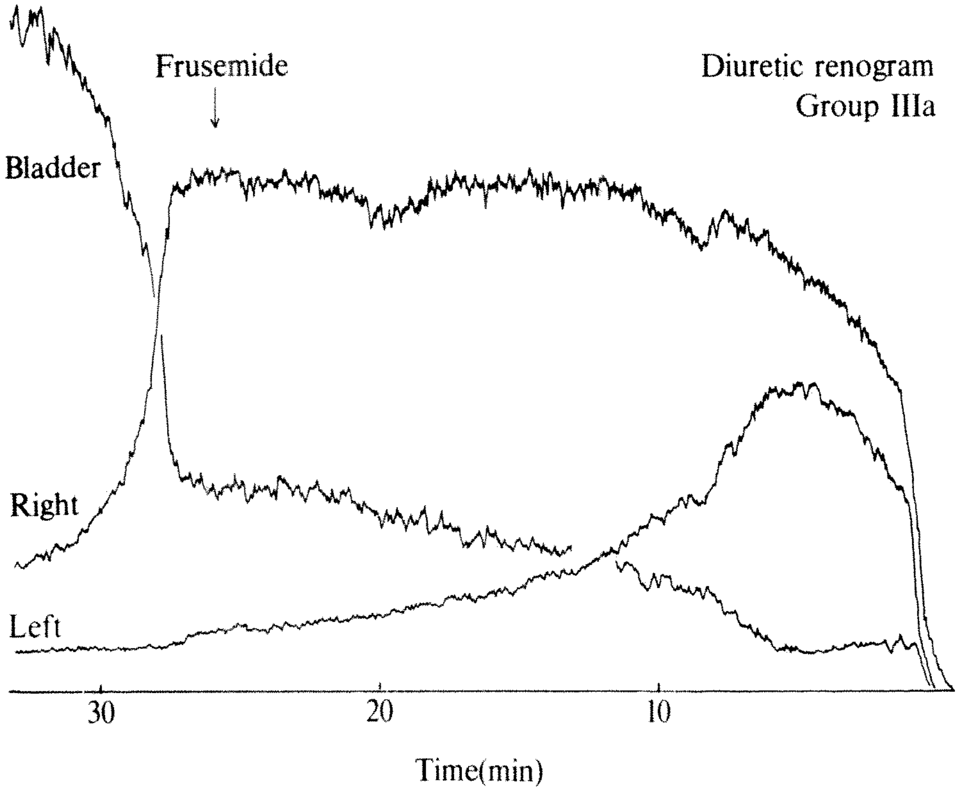

Fig. 3 Group IIIa response. An initially obstructive pattern on the right with rapid excretion after Frusemide.

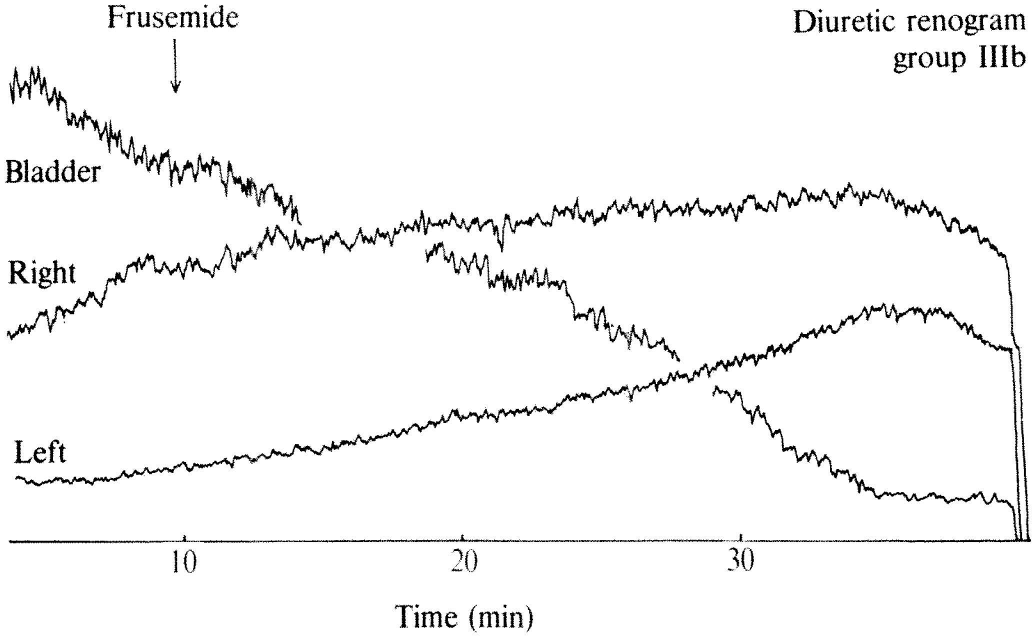

Fig. 4 Group IIIb response showing an initially obstructive tracing over the right kidney and a partial improvement in excretion after Frusemide.

scopy included a reduction in the complement of myofilaments (Fig. 5) and the development of unusually large quantities of granular reticulum and Golgi membranes. In all affected cases these structural abnormalities were found uniformly throughout the distended segment of the upper urinary tract. There was no gradation of degree of abnormality found in the involved segment and the changes ceased abruptly in the non-distended parts of the specimen.

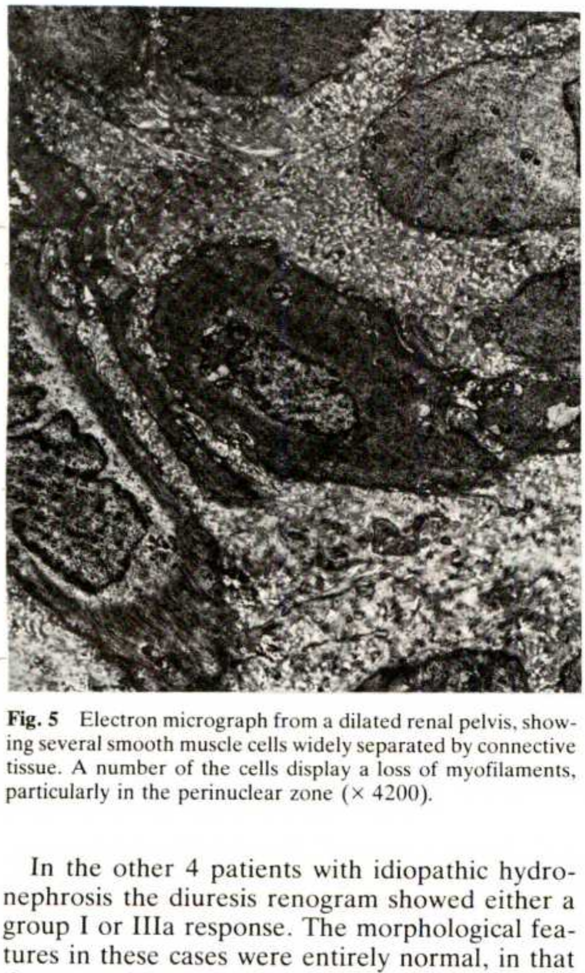

Fig. 5 Electron micrograph from a dilated renal pelvis, showing several smooth muscle cells widely separated by connective tissue. A number of the cells display a loss of myofilaments, particularly in the perinuclear zone (× 4200).

In the other 4 patients with idiopathic hydronephrosis the diuresis renogram showed either a group I or IIIa response. The morphological features in these cases were entirely normal, in that they were identical to those of the control tissue (Fig. 6).

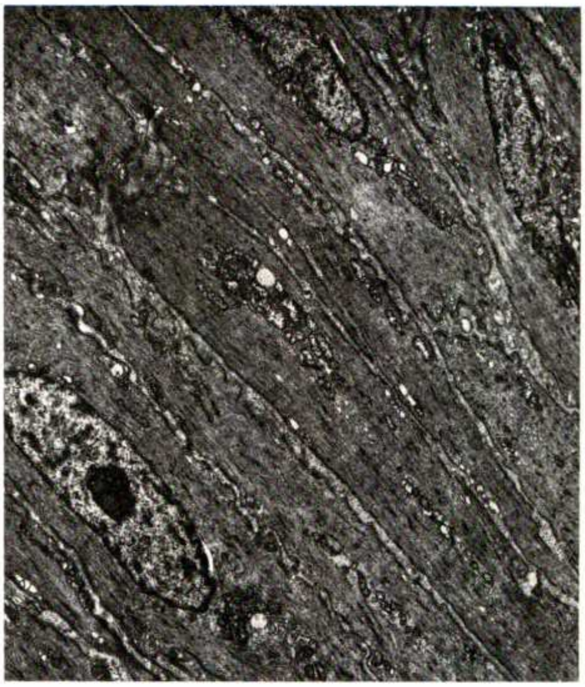

Fig. 6 Electron micrograph of smooth muscle cells from a non-dilated renal pelvis. The cells are closely packed together with relatively little intervening connective tissue and each cell contains abundant myofilaments (× 4200)

Table 3 Idiopathic Hydronephrosis—Diuresis Renogram

Affected Kidney	*Opposite Kidney*	
Obstructed	IIIa (Hypotonic)	1
	Equivocal	1
	Flat elimination (Bulky pelvis on IVU 2)	4
	Normal	15
Hypotonic	Previous nephrectomy	1
	Normal	3

A further observation made in this study was the assessment of the excretory ability of the contralateral kidney. In patients with idiopathic hydronephrosis (Table 3) there was one patient in whom an obstructed diuresis renogram was found on the left side and an equivocal pattern on the right. Bilateral pyeloplasties were performed and morphological changes were found in both specimens. In another case there was a IIIa (hypotonic) diuresis renogram pattern on the side opposite a partically obstructed (IIIb) kidney.

Discussion

Dilatation of the upper urinary tract in the absence of obstruction is a well recognised phenomenon (Shopfner, 1966; Bäcklund and Reuterskiöld, 1969; Whitaker, 1975). Impairment of renal function associated with marked dilatation of the upper tract is usually assumed to be caused by obstruction if intrinsic renal disease, gross persistent infection and vesicoureteric reflux have been excluded (Whitaker, 1973).

It has previously been suggested that the diuresis renogram distinguishes between obstructive and non-obstructive dilatation of the renal pelvis and ureter (O'Reilly *et al.*, 1978). Group I cases are renographically normal, despite a minor degree of dilatation found on intravenous urography, and thus it is felt that obstruction is excluded in these cases. Group II and IIIb responses are thought to represent a genuine obstruction of the upper urinary tract. A group IIIa response is believed to indicate a mixing chamber effect in the dilated renal pelvis, the initial impairment of elimination being due to radioisotope stasis, but the effect of Frusemide producing rapid excretion in the absence of a genuine impedance to flow.

The present study has divided patients with radiologically demonstrated idiopathic hydronephrosis into 2 broad categories. The exclusion of obstruction on diuresis renography was associated with normal renal pelvic morphology. Abnormal structural features were, however, found in the renal pelves of cases in which the diuresis renogram showed obstruction or poor function. This correlation supports the view that the diuresis renogram is an accurate method of distinguishing between these 2 seemingly different groups of patients with suspected pelviureteric function obstruction.

No definite correlation has been found in cases of obstructive hydronephrosis between the degree of structural abnormality and the age of the patients or the length of history. Neither can a consistent relationship be demonstrated between the degree of obstruction demonstrated on diuresis renography and the severity of the morphological changes in these patients.

In conclusion, there is a good correlation between the results of the functional diuresis renogram and the morphological studies outlined here. This study has also raised some important questions concerning the aetiology of pelviureteric junction obstruction. Is hypotonic dilatation of the renal pelvis in patients with normal morphological features a different disease entity from the established pelviureteric junction obstruction with abnormal structural findings; alternatively, are the 2 groups different stages of the same disease process? These unexplained problems may be further clarified by a study designed to follow the evolution of hypotonic upper urinary tract dilatation and to assess its long-term effects on renal function.

Acknowledgements

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The Intravenous Urodynamogram

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Summary—Modifications to the intravenous urogram are described. It is suggested that the time has come to rationalise the standard procedure.

If an evaluation of the lower urinary tract is required, the voiding films may be modified to provide an intravenous urodynamogram.

If an evaluation of the upper urinary tract is directed at a specific question, then the number of spot-films can often be reduced.

Many investigative procedures are, of necessity, a compromise. Few have to be more arbitrary than the spot-film record of an intravenous urogram (IVU) series. An IVU seeks to select a few representative snapshots of the passage of a bolus of contrast through the kidney and the urinary tract; the natural passage of this, from injection to voiding, usually takes from 1 to 4 h, depending upon the bladder function.

Over the years intravenous urography has been mainly directed towards providing an acceptable impression of the pelvicaliceal anatomy and the overall function of the urinary tract; the timing of the spot-films has been selected to cover the majority of clinical circumstances for which the investigation is routinely requested. The information that a standard IVU series provides about the lower urinary tract is strictly limited and it is accurate only within the context of its performance. Increasing awareness of the significance of lower urinary tract dysfunction in many clinical problems and of the shortcomings involved in attempting to evaluate these by simple deduction from endoscopic appearances has resulted in the need for the addition of simple urodynamic studies in the routine investigation of many patients.

It is clear that the full potential of the information relating to lower urinary tract function and dysfunction that is available from intravenous urography is not recorded by the currently accepted routine procedure; 2 questions therefore arise:

1. Whether, as a routine screening procedure in some referral centres, there might be practical advantages in extending it to a more appropriate functional study of the lower urinary tract.
2. Whether it might be reasonable to reduce the number of upper tract spot-films in the screening routine of many conditions.

The Basic Study of Voiding Efficiency

A residual urine seen on the post-voiding film of a standard IVU, taken some 40 min after the injection, may or may not be representative of the patient's normal post-voiding state because some patients are unable to initiate effective voiding until their bladders are full. However, the presence of such a residual usually leads to further investigation which may or may not be necessary.

An appropriate evaluation of voiding efficiency should therefore take place when patients feel that their bladders are fully distended to a point at which they would normally take active steps to void; at this point a spot-film will indicate the size and configuration of the full bladder and another film taken after evacuation of a normally full bladder in private is a fair indication of the normal state of affairs. Both these films are likely to provide information of clinical value but, while a significant residual urine under these circumstances certainly requires urodynamic evaluation, an absent residual urine by no means excludes a significant or even a severe degree of obstruction in the male (Turner-Warwick *et al.*, 1973a).

The voiding process is, of course, a complicated one and in some cases detailed evaluation of it by

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synchronous pressure-flow cystourethrography is appropriate. However, bearing in mind its limitations, the simple record of the voiding flow pattern from a full bladder is probably the most useful single screening test of voiding efficiency; obtained in the privacy of a toilet it readily distinguishes the excellent or good unimpeded stream and also the much prolonged and perhaps intermittent obstructed stream. In between these there are, of course, some intermediate patterns that may or may not require pressure-flow evaluation according to the particular problem (Turner-Warwick *et al.*, 1973b).

The basic concept of the *intravenous urodynamogram* is that, in addition to the basic upper tract spot-films:

1. The lower tract films should be postponed until the patient feels that the need to urinate is a matter of urgency, at whatever time after the initial contrast injection.
2. A spot-film is taken immediately before and after voiding.
3. A voiding flow pattern and a voiding volume are recorded and form an integral part of the record of the examination.

The intravenous urodynamogram seems to be an appropriate screening test for the identification and the exclusion of urinary tract dysfunction in the investigation of many clinical symptoms such as frequency, urgency, nocturia in the absence of infection, nocturnal enuresis and incontinence and also in the investigation of recurrent urine infection or suspected outflow obstruction.

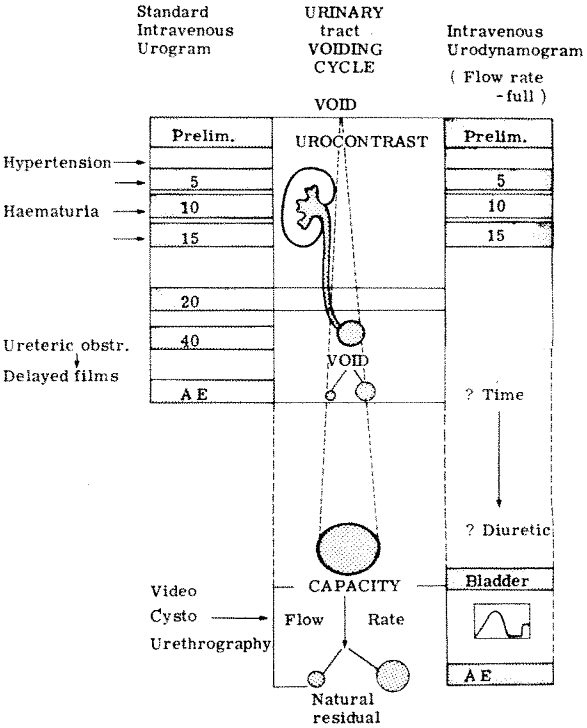
The IV urodynamogram will generally indicate whether there is an upper tract problem that requires more detailed intravenous or direct urographic studies, or a lower tract problem that requires more detailed urodynamic study. Many cases certainly require routine endoscopic evaluation in addition, but in some cases the functional information provided by the dynamogram may make this unnecessary.

Modified and Extended Intravenous Urographic Series

In recent years the rational use of intravenous urography to resolve specific clinical questions has led to the development of a number of modified techniques. Thus, before the patient leaves hospital after an upper urinary tract reconstructive procedure, it may be helpful simply to know that the kidney is draining satisfactorily; a routine IVU series is obviously excessive when all that is necessary is a single film, taken without preparation, at an appropriate interval, say 20 min, after an injection.

Another example of a specifically modified intravenous urographic series is the immediate urography for suspected ureteric colic. The limitations of the use of plain films are well recognised; the practical question that needs to be answered is whether a clinically suspicious pain is or is not associated with ureteric hold-up, irrespective of whether a calculus is seen or not. If an intravenous urogram taken while the patient actually has the pain demonstrates neither urinary hold-up nor delayed excretion, then the diagnosis of ureteric colic must be held in doubt. The "Casualty Officer's" IVU is modified to determine just this and no more. It is an immediate procedure, taken without preparation while the patient still has pain. In many cases a plain X-ray and a 20-min film are all that is necessary, while in others delayed films after voiding to remove a bladder shadow overlying the lower end of the ureter may be required.

The investigation of some specific conditions requires spot-films in addition to the standard series. In hypertension, for instance, the early



progress of the nephrographic phase may be important, while in the search for the origin of haematuria special attention must be paid to pelvicaliceal anatomy, while delayed films may be required to demonstrate a particularly capacious or partially obstructed urinary tract.

Thus already there is a rational trend towards adapting the intravenous urogram to specific clinical problems and the logical extension of this, in some referral centres, might be to reduce the number of spot-films in the basic screening procedure which accounts for the majority of the departmental work-load. A fairly typical example of a standard urographic series includes a full-length plain film, 3 renal area views at 5, 10 and 15 min, a full-length 20-min film, another at 30 min followed by a post-voiding film of the bladder area: a total of 6 or 7 films taken within a period of 45 min. The advantage of such a standard series is that, provided the radiologist has been properly forewarned of the need for specially extended studies, few patients need to return for repeat studies.

On the other hand, it is well recognised that the yield of unexpected findings on routine urographic screening is poor in many conditions, such as enuresis in children, urinary tract infections, incontinence in females and suspected outflow obstruction in both males and females. However, few clinicians would be happy to treat these conditions without a urographic check.

The basic minimum of upper tract spot-films of an IVU screening study would obviously be a full-length preliminary film and a full-length upper tract film at, say, 15 min; in most cases this would answer the basic clinical questions. Are major calculi present? Are both kidneys and upper tracts present and grossly normal?

In practice the economy of such a minimal series might prove self-limiting and result in a disproportionate number of repeat studies, so that the addition of a 5-min renal area film would seem to have advantages. The actual selection of the upper tract series would naturally be, as it is at present, at the discretion of individual departments; the important thing is to raise the query.

Quite apart from the obvious reduction of irradiation, the economy on films, and the appropriate evaluation of the lower urinary tract that it provides, the modification of the upper tract spot-film series might enable several patients to be processed simultaneously on one X-ray table by taking their spot-films in appropriate consecutive rotation; once these have been taken the patient could be sent away to drink and return when the bladder is full for the pre- and post-voiding films. It is not essential to check the voiding flow pattern at the time of this particular voiding but in a urodynamic unit such as ours, where the equipment is immediately available, it is often convenient, especially for long distance referral patients, and occasionally there may be particular advantages in the correlation of the records on the same voiding. Also on occasion there may be a place for the judicious use of a diuretic to speed up the voiding studies after re-hydration, especially when the patient is an infrequent voider.

"What is the Purpose of this Investigation?"

In the practice of our urological department over the course of a year or so, we have usually found it quite easy to decide whether we wish to request a screening urodynamogram or a modified or extended intravenous urogram.

Some years ago, as a direct result of the particularly close clinical liaison and the joint meetings that our urological department holds with our department of radiology, the request form for all our hospital X-rays was modified to include a space below the "Clinical Summary" headed "What is the Purpose of this Investigation?" This single change seems to have resulted in improved clinical communication and co-operation. So far as urography is concerned, the "Investigation Requested" is either an intravenous urogram or an intravenous urodynamogram; these are appropriately booked in separate X-ray sessions. If a modified or an extended intravenous urogram is requested, the purpose of the examination makes it possible for the radiologist to adjust the spot-films on the series appropriately in the X-ray session that is devoted to intravenous urography.

Many patients are referred to a urodynamic centre from hospitals lacking the facility for even basic urodynamic evaluation and urodynamic dysfunction is extraordinarily difficult to identify or exclude clinically in many cases. We have found it most helpful, particularly for long distance referrals, to run an intravenous urodynamogram morning session, followed in the afternoon by a full urodynamic evaluation session with video pressure-flow cystourethrography; when in doubt about the possible need for full urodynamic evaluation we book the patient for an intravenous urodynamogram in the morning and use this to decide whether detailed urodynamic investigation is necessary.

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Surgical Treatment of the Massively Dilated Primary Megaureter in Children

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Summary—From 1964 to 1975, of 83 children with primary megaureter 33 had unilateral and 8 bilateral massively dilated ureters that required surgical treatment, and of these 73% had febrile infection, 5% were septic and 10% were azotaemic.

Surgical treatment consisted of ureteric reimplantation with excision of the atonic distal segment, preceded by diversion when indicated. Tailored reimplantation was successful in 98% of ureters and non-tailored reimplantation was uniformly unsuccessful. All failures were successfully corrected by tailored reimplantation.

Thus the requirements for successful surgical management of massive ureteric dilatation in children secondary to an atonic distal ureteric segment are excision of the atonic segment, transvesical or extravesical tailoring of the ureter and reimplantation.

Primary megaureter or functional obstructive megaureter, first described in 1923 (Caulk, 1923) is most appropriately defined as a congenitally dilated ureter which is secondary to no pathology other than an atonic distal ureteric segment, and unassociated with intrinsic obstruction of either ureter or urethra, or vesicoureteric reflux. The trigone and ureteric orifices are endoscopically normal. The ureter is dilated down to a distal funnel or beak-shaped termination and is more dilated distally than proximally (Pitts and Muecke, 1974). A trickle of dye may be seen traversing the distal atonic segment in a post-micturition IVP film, especially in an oblique view (Fig. 1). Fluoroscopic examination at this time demonstrates active peristalsis in less dilated primary megaureters but active peristalsis ends and reverse peristalsis begins at the atonic segment (Pfister *et al.*, 1971).

The atonic segment, which ranges in length from 0.5 to 4 cm and which is in the ureter just proximal to the intravesical portion of the ureter, consists of hypoplastic and atrophic muscle fibres with intervening fibrosis (McLaughlin *et al.*, 1973; Hanna *et al.*, 1976). The muscle at the junction between the dilated and non-dilated segment is also abnormal (Tanagho *et al.*, 1970). The muscle of the dilated ureteric segment is hypertrophied (Tanagho *et al.*, 1970; McLaughlin *et al.*, 1973). The aetiology of primary megaureter is controversial. It has been produced in the fetal lamb ureter by wrapping it with a plastic tube (Tanagho, 1974), suggesting that the arrest of ureteric lengthening in the distal ureter may be responsible as this is the last portion of the ureter to develop its muscular arrangement.

Patients and Methods

From August 1964 to April 1975, 83 children with primary megaureter were cared for at The Hospital for Sick Children, Toronto. Of this group there were 49 massively dilated ureters in 41 children in whom symptoms or impaired renal function indicated surgical treatment. (Of the others, those with normal parenchyma and without pyelocaliectasis have been observed and remain stable and asymptomatic; those with mild ureteropyelocaliectasis underwent non-tailored reimplantation.) The 49 massively dilated primary megaureters are the subject of this review. They presented most commonly with urinary tract infection (Table 1). Seventy-three per cent presented with febrile urinary tract infection, severe in 5%. Ten per cent were azotaemic at the time of presentation. The ratio of males to females was approximately 3:1. In 24% the condition was bilateral and in 5% associated with other contralateral congenital abnormalities (Table 2).

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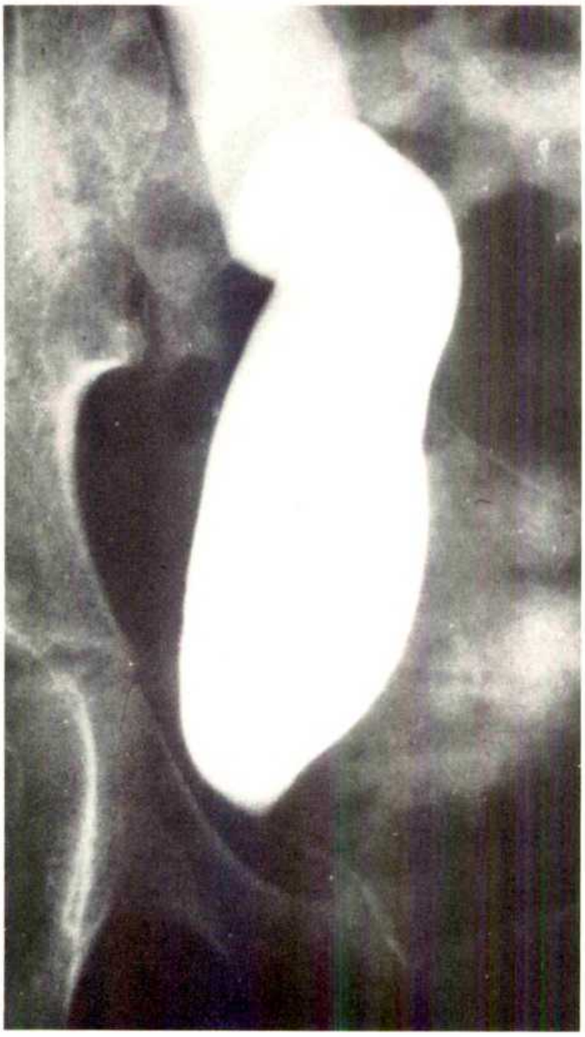

Fig. 1 Post-micturition film demonstrating distal portion of massively dilated primary megaureter with trickle of dye traversing distal atonic segment.

The age of presentation ranged between 2 weeks and 14 years (mean 4 years 3 months).

Table 1 Clinical Presentation in 41 Children with Massively Dilated Primary Megaureter

Febrile urinary tract infection	30 (73%)
Systemic sepsis	2 (5%)
Haematuria	7 (17%)
Abdominal pain	4 (10%)
Abdominal mass	2 (5%)
Azotaemia	4 (10%)

Table 2 Findings in 41 Children with Massively Dilated Primary Megaureters

Unilateral in 33, bilateral in 8			
Sex incidence:	31 males	10 females	
Side	left 30	right 19	
Contralateral abnormalities in unilateral cases			
mild primary megaureter			2
massive reflux			1
agenesis			1

The surgical treatment of the massively dilated primary megaureter consisted of ureteric reimplantation with excision of the atonic distal segment (Flatmark *et al.*, 1970; Williams and Hulme-Moir, 1970; McLaughlin *et al.*, 1971). This was generally combined with transvesical or extravesical tailoring over a variable length (Rabinowitz *et al.*, 1977b). If indicated, temporary nephrostomy was carried out before reconstruction (Rabinowitz *et al.*, 1977a, b). Follow-up has included physical examination, urinalysis, urine culture and sensitivity, intravenous urogram, voiding cystourethrogram and renal function studies. These children have been followed up from 1 to 11 years with an average length of pyelographic follow-up of 5 years. To classify a surgical procedure in these children as a good result, it had to meet all of the following criteria: the intravenous urogram showed significant improvement, there was no evidence of reflux, renal function did not deteriorate, and infection was absent. If any of these criteria were not met, the surgical treatment was classified as unsuccessful.

Results

Of the 49 massively dilated primary megaureters, 3 were removed as the primary procedure (Table 3), one because the child was retarded and had a normal contralateral kidney, and 2 because of non-function on urogram and scan.

Forty-one ureters were treated by excision of

Table 3 Surgical Treatment of 49 Primary Megaureters

Nephroureterectomy		3
Excision of atonic segment and ureteric reimplantation		42
With lower ureteric tailoring	41	
With preliminary nephrostomy	19	
With upper ureteric tailoring	3	
Cutaneous ureterostomy		4
With excision of atonic segment and ureteric reimplantation	4	
With lower ureteric tailoring	3	

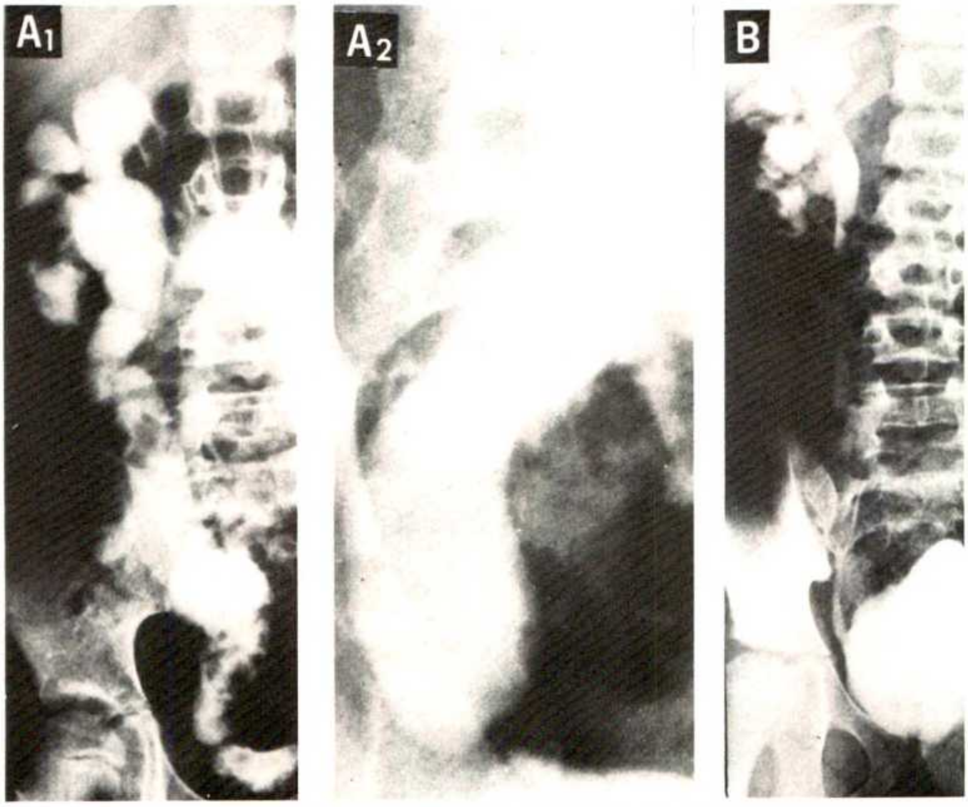

Fig. 2 Case J.M. Seven-year-old female presented with febrile *E. coli* urinary tract infection. A1 and A2: IVP demonstrating right ureteropyelocaliectasis secondary to atonic lower segment. B: IVP 4 years after transvesical tailoring and reimplantation. Uninfected on no medication. No reflux.

the atonic segment and primary extravesical or transvesical tailoring and reimplantation (Fig. 2). Nineteen had a nephrostomy for a period of 1 to 10 weeks before the tailoring procedure because the children were severely infected or azotaemic, or because the surgeon was reluctant to carry out an extensive tailoring procedure without proximal diversion (Fig. 3). Forty reconstructions were uniformly successful by all parameters. The one failure, a ureter that was obstructed post-operatively, was corrected by re-operation, but is regarded as a failure in this series.

Temporary proximal diversion by non-intubated cutaneous ureterostomy was carried out 4 times but tailoring and reimplantation were still required in the subsequent reconstruction and were uniformly successful.

Two massively dilated ureters were reimplanted without tailoring, one after temporary nephrostomy and the other after temporary cutaneous ureterostomy (Table 4), because both appeared to have improved to such an extent with diversion that a tailoring procedure seemed unnecessary. Both refluxed post-operatively and both had pyelographic deterioration with refractory infections, confirming that any adequate assessment of the calibre of the decompressed primary megaureter is extremely difficult at the time of surgery. Although both failures were later successfully treated by tailoring and reimplantation, they are regarded as failures.

Table 4 Results of Surgical Reconstruction of Massively Dilated Primary Megaureter

	Tailored reimplant	*Non-tailored reimplant*
Reconstruction	44	2
IVP: marked improvement	37 (84%)	
improved	6 (14%)	
deteriorated	1 (2%)	2
No reflux	44 (100%)	0
Infection free	43 (98%)	0
Good result	43 (98%)	0

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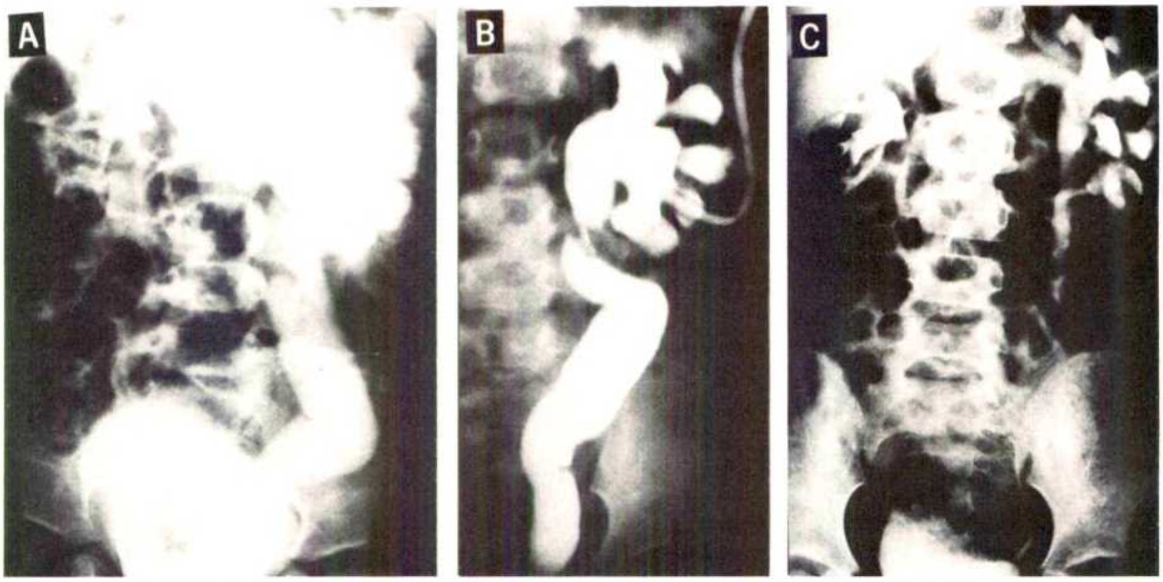

Fig. 3 Case J.K. Eighteen-month-old female with *E. coli* septicaemia. A: IVP demonstrating left ureteropyelocaliectasis secondary to atonic lower segment. B: Nephrostogram 6 weeks after nephrostomy. C: IVP 4 years after transvesical tailoring and reimplantation. Uninfected on no medication. No reflux.

Discussion

In reviewing our results of surgical treatment of massively dilated primary megaureters in children, tailored reimplantation was successful by all criteria in 98% of ureters and non-tailored reimplantation was uniformly unsuccessful. The 3 ureters classified as failures after initial reconstruction were all corrected by a second surgical procedure. Thus it is apparent that the absolute requirement for successful surgical management of massive ureteric dilatation in children secondary to an atonic lower segment is excision of the atonic segment, transvesical or extravesical tailoring and reimplantation. If preliminary diversion is required, nephrostomy is more appropriate than cutaneous ureterostomy. The degree of ureteric tortuosity is rarely enough to warrant long-term diversion by cutaneous ureterostomy. Finally, the ureter must be tailored whatever the apparent reduction in its calibre with temporary diversion. If these principles are followed, the success rate of surgical management of massively dilated primary megaureters should exceed 95%.

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A Double Blind Trial of Bromocryptine in the Treatment of Idiopathic Bladder Instability

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Summary—Fifty-one patients (aged 20 to 68 years) entered a 6-week double-blind trial of Bromocryptine, a dopamine agonist. All patients complained of the complex: frequency, nocturia, urgency and urge incontinence which was due to demonstrable bladder instability. No significant improvement in either symptoms or cystometric findings was seen in the Bromocryptine treated as compared with the control group. A high incidence of nausea was noted in the treated groups. The results of this study suggest that Bromocryptine does not have a therapeutic role in the treatment of idiopathic bladder instability.

Bladder instability is a common cause of lower urinary tract symptoms. The symptoms of frequency, nocturia, urgency and urge incontinence are often due to the waves of detrusor contraction occurring during bladder filling, which are characteristic of the unstable bladder. Bladder instability may be associated with a known cause, *e.g.* neurological disease, infection or outlet obstruction, or the instability may be idiopathic.

Idiopathic bladder instability remains a difficult therapeutic problem. General advice, such as restriction of oral fluids, particularly in the evening, will be sufficient only for those patients with mild instability. Medical treatment is usually the next line of therapy. Anticholinergic drugs have been most fully assessed. The main problem with this group of compounds is that to produce an adequate effect on the bladder, unwanted side effects result, *e.g.* dryness of mouth and blurred vision. Farrar (Farrar and Pryor, 1976; Farrar and Osborne, 1976) has published 2 preliminary communications on the efficacy of the dopamine agonist, Bromocryptine (CB 154 Sandoz), in patients with lower urinary tract symptoms. In the first (Farrar and Pryor, 1976), Bromocryptine improved the symptoms of patients with benign prostatic hypertrophy. In particular, the symptoms of frequency, nocturia, urgency and urge incontinence, usually associated with bladder instability, were improved. This led to Farrar's second study (Farrar and Osborne, 1976) in which Bromocryptine was given to 24 patients with idiopathic instability. In a partially controlled study Bromocryptine therapy again appeared to result in symptomatic improvement, although patient numbers were too small to allow statistical confirmation of benefit.

Bromocryptine is a dopamine receptor stimulator, and as such finds an increasing number of clinical uses. In patients with hyperprolactinaemia it is used to achieve fertility, treat galactorrhoea and to suppress lactation. Bromocryptine is also used to treat Parkinson's disease and acromegaly. As well as being widely distributed in the brain, dopamine is found associated with the peripheral nervous system (Thorner, 1975). Farrar and Osborne (1976) suggested that Bromocryptine might suppress bladder overactivity, either by modulating cholinergic transmission or by acting directly.

The trial, described below, was designed to assess further the role of Bromocryptine in treating idiopathic bladder instability.

Patients and Methods

Fifty-one patients, 6 men and 45 women (aged 20 to 68 years), entered a 6-week double-blind trial of Bromocryptine. All patients were complaining of lower urinary tract symptoms. Their symptomatic complaints of frequency, urgency and urge incontinence were shown by inflow cystometry to be due to bladder instability. In all cases every effort was made to exclude the known causes of instability. In particular, neurological

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Table 1 Symptom Score of Symptomatic Complaints

Symptom		*Symptom score (possible range 0-10)*
Frequency	<7	0
	7-9	1
	>9	2
Nocturia	0	0
	1-2	1
	3+	2
Urgency	none	0
	slight	1
	marked	2
Urge incontinence	none	0
	occasional	1
	frequent	2
Enuresis	never	0
	occasional	1
	frequent	2

abnormalities were excluded, as far as is possible, by a careful physical examination, and obstruction was excluded by a pressure-flow analysis of micturition. In addition, no patient with a history of peptic ulceration or of hypertension was admitted to the trial as it is possible that Bromocryptine might have exacerbated either condition.

The symptomatic complaints and results of urodynamic investigations were recorded prior to the trial's commencement. The symptomatic complaints were recorded as a symptom score as shown in Table 1. The degree of bladder instability was recorded as the instability index (Fig.). The techniques of the urodynamic investigations were similar to those previously fully described (Abrams *et al.*, 1976). The patient was then entered into the trial in which the active drug and the placebo were presented in an identical tablet. The patients were instructed to take their tablets with food and to increase the dose gradually until the full regime was achieved after 7 days. On days 1 and 2 half a tablet was taken at night, on days 3 and 4 one tablet at night, on days 5 and 6 one tablet at midday and one at night, and from day 7 onwards one tablet at midday and 2 at night. This gave a full dosage of Bromocryptine of 7.5 mg per day. Patients were instructed that in the event of side-effects they should go back to the previous step and then proceed with increasing dosage as before. They were also requested to record all side-effects and to contact the trial organisers if side-effects were troublesome.

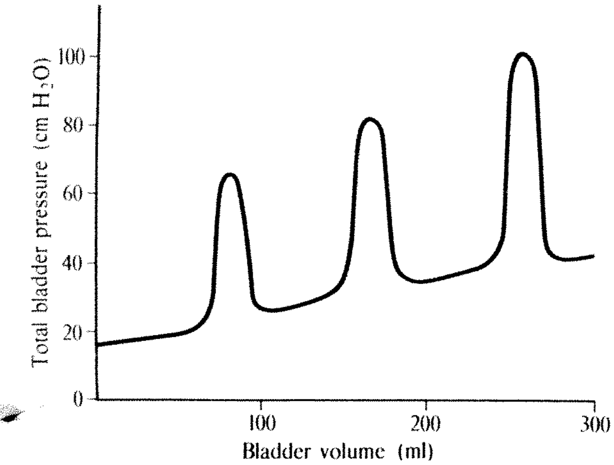

Fig.

At the end of the 6-week trial period the patients were interviewed, their symptoms and any side-effects recorded, and their urodynamic studies repeated.

Urine culture, routine haematological and routine biochemical tests were performed before and after the trial.

Results

Fifty-one patients started the trial and 38 completed the 6-week trial period. Twenty-five patients were on the active drug and of these 10 patients withdrew for the following reasons: 5 due to nausea, 1 to a vasovagal attack which the patient attributed to the drug, 1 due to loss of energy and 3 patients were lost to follow-up. Twenty-six patients took placebo therapy and only 3 withdrew; 1 patient's symptoms got worse, 1 became involved in criminal proceedings and 1 patient was lost to follow-up.

The results have been assessed by analysis of the symptomatic and cystometric changes occurring during the course of the trial. Table 2 shows the patients' overall opinion of their symptomatic improvement or otherwise. There was no significant difference between the 2 groups either on the patients' assessment or on the semi-objective criteria of symptom score (given in brackets in Table 2).

The second cystometrogram at the end of the 6-week period showed few changes (Table 3). Five patients showed reversal of bladder instability and this was accompanied by symptomatic improvement in 4 of the 5; the remaining patient's

Table 2 Patients' Symptomatic Assessment

	Drug group *(25 patients)* (symptom scores in brackets)	*Placebo group* *(26 patients)* (symptom scores in brackets)
Better	6 (6)	7 (6)
Slightly better	3 (3)	4 (5)
No difference	9 (9)	11 (10)
Worse	0 (0)	1 (2)
Assessment not possible	7	3

main complaint was of enuresis and this symptom remained unchanged. There was no significant difference in the incidence of instability reversal between the 2 groups. Analysis of instability indices before and after the trial also showed no difference between the groups.

Side-effects were noticed by 13 patients, all of whom were in the Bromocryptine group; 11 complained of nausea which forced 5 patients to withdraw from the trial, 1 patient complained of headaches and 1 of severe vasovagal attack.

No changes in the basic haematological and biochemical blood tests were noted in either group.

Discussion

The demonstration of bladder instability during bladder filling should be interpreted in the light of the patients' symptomatic complaints. The patient usually appreciates a desire to void, or urgency, during an unstable wave. However, cystometrography is an unphysiological investigation. One should therefore ask whether or not the investigation itself is responsible for inducing instability: in some patients it undoubtedly is. Therefore during investigation, and particularly during an unstable wave, the patient should be asked whether this is the sensation of which he or she is complaining. It is then that the cystometric findings and the symptomatic complaints should achieve a good correlation. In this series it was established at the onset of the trial that each patient's symptoms were due to demonstrable instability.

Table 3 Cystometric Changes

	Drug group		*Placebo group*	
	Stable	*Unstable*	*Stable*	*Unstable*
Pre-trial	0	15	0	23
Post-trial	2	13	3	20

This study illustrates the fluctuating nature of lower urinary tract symptoms. This has been previously noted in male patients with "prostatism" (Abrams, 1977). In the present series 50% of all patients were either much better or slightly better over the 6-week period, the percentage being identical in both the Bromocryptine and the control group. This improvement may be due to a real change in bladder activity, and this is suggested by the 5 patients who had stable bladders at the end of the trial and who were symptomatically improved. However, most patients remained unstable (33 of 38) and their instability indices showed the degree of instability to be unchanged. In these patients improved symptoms are likely to be due to their restricting fluids and avoiding alcohol and its diuretic effect. Although Farrar and Osborne (1976) had demonstrated instability in all patients at the start of the trial, the cystometrograms were not repeated at the end of the study period. The figure of a 50% symptomatic improvement in the Bromocryptine group is the same in both groups in the present study and identical to that of males with "prostatism" on placebo therapy (Abrams, 1977). It is interesting to note the good correlation between the patients' own assessment and the symptom score value. This close agreement is no doubt helped by providing the patients with frequency charts on which day and night frequency are recorded before the trial and in its last week.

It is disappointing that Bromocryptine did not help this difficult group of patients, but the study does demonstrate how many patients will be helped by general advice, the clinician's interest and the passage of time. The drug dosage of 7.5 mg per day was higher than the 5.0 mg per day used by Farrar and Osborne. The side-effect of nausea was also noted by Farrar and Osborne (1976), but the problem of constipation, which they saw, was not a feature of our trial. The incidence of nausea (11 of 25) probably means that Bromocryptine could not be given in a higher dosage.

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The Role of Internal Urethrotomy in the Prevention of Urethral Stricture following Transurethral Resection of Prostate

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Summary—Urethral stricture is the commonest late complication of transurethral prostatectomy. Although internal urethrotomy is widely practised to prevent strictures, there are no reports of any controlled trials of the procedure.

A prospective trial of internal urethrotomy, using the Otis urethrotome, in 210 consecutive transurethral prostatectomies is presented. Patients were divided into 2 groups, those undergoing urethrotomy before TUR ("Trial group") and those undergoing TUR without urethrotomy ("Control group"), and they were followed for a minimum of 6 months. The incidence of stricture in the control group was significantly greater than in the trial group ($P < 0.01$).

Analysis of all other variables revealed no difference between the 2 groups and it is concluded that internal urethrotomy does prevent stricture formation and that it should be undertaken routinely before transurethral resection.

Urethral stricture is the commonest late complication of transurethral prostatectomy, the incidence in published series varying between 4 and 12% (Warres, 1958). Several measures have been suggested to prevent stricture formation including perineal urethrotomy, pre-operative urethral dilatation (Lentz *et al.*, 1977) and internal urethrotomy (Emmett *et al.*, 1963; Blandy, 1971). Although internal urethrotomy is widely practised, there have been no controlled trials published to assess the efficacy of this procedure. We have therefore undertaken a prospective controlled trial of internal urethrotomy.

Patients and Materials

Patients undergoing transurethral prostatectomy under the care of one consultant urologist were studied. They were divided into 2 groups, the trial group undergoing pre-operative internal urethrotomy, the control group pre-operative urethral dilatation. Patients were allocated into one or other group according to the day of the week on which surgery was performed.

In order to show that the 2 groups were comparable in all other respects, we studied the following factors: age of patient, duration of symptoms, presence of urinary tract infection, whether the operation was an elective or an emergency procedure, duration of pre-operative and post-operative catheterisation, blood urea, weight and histology of prostate resected, size of resectoscope sheath used, and the size of catheter used post-operatively.

Transurethral prostatectomy was performed for the usual indications under general or epidural anaesthesia. The penis was cleaned with 1:2000 aqueous hibitane solution and the urethra disinfected with 1% xylocaine and hibitane jelly. Preliminary cystoscopy was carried out in all cases using a 22 FG cystoscope.

Patients in the control group were then dilated to 26/30 FG, whilst patients in the trial group underwent full length internal urethrotomy with the Otis urethrotome set at 30 FG. The urethrotome was passed closed and then opened to 30 FG. The blade was exposed and a full length 2 mm deep incision made at 12 o'clock by withdrawing the instrument.

Resection was performed using the 24 FG or 27 FG Storz or the 26 FG genitourinary resectoscope. Irrigation during surgery was with 1 to 5% glycine solution.

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

Following resection, a self-retaining Simplastic or reinforced latex catheter was passed and left *in situ* for 48 h or until the urine was free of blood. A diuresis was maintained with Bumetamide and intravenous fluids to reduce the incidence of clot retention. Regular urine cultures were performed and bacteriologically proven infection was treated with the appropriate antibiotic. Following discharge, patients were seen in the out-patient clinic at 1, 3, 6 and 12 months. Any patient with symptoms suggestive of a stricture was admitted for urethroscopy.

Results

Two hundred and ten patients were studied, 108 in the trial group and 102 in the control group. In the trial group 4 patients died of causes unrelated to surgery and 4 patients failed to complete follow-up. In the control group, 7 patients died within the follow-up period and 5 patients failed to complete follow-up. Thus there were 100 patients in the trial group and 90 in the control group available for study.

Of the 100 patients in the trial group, only 2 had symptoms suggestive of a stricture and neither patient had a stricture on urethroscopy. Of the 90 patients in the control group, 12 developed symptoms of a stricture and on urethroscopy 9 of them were shown to have developed a stricture. The difference in stricture rate between the 2 groups was significant using the χ^2 test (Table 1). The sites of the strictures are shown in Table 2.

In analysing the other factors studied, we have tried to show 2 things: firstly that there was no factor which differed between the 2 groups and secondly that there was no factor in the patients developing a stricture that could be used to identify a high risk group. In order to do this, we have presented the data in terms of the trial group and the control group, subdivided into those patients with and those without a stricture. The mean age ± standard deviation for blood urea and pre-operative duration of symptoms showed no differences between the groups. Similarly, the percentage of patients undergoing surgery for acute or acute on chronic retention in the trial and the control groups was not significantly different. The percentage of patients in each group with infected urine pre-operatively, per-operatively and 1 month post-operatively is shown in Figure 1. The 11% incidence of post-operative infection in the control group patients developing a stricture represented only 1 patient and again, there was no statistically significant difference.

Table 1 Incidence of Stricture

	Number (N)	*Patients developing stricture*	
Trial group	100	0	0%
Control group	90	9	10%

$\chi^2 = 9.5 \quad P < 0.01$.

Table 2 Site of Stricture in 9 Patients

External meatus	2
Navicular fossa	3
Peno-scrotal	1
Membranous	4
Total	10

(One patient had 2 strictures, membranous and navicular fossa.)

The duration of pre-operative catheterisation showed an even distribution between the groups (Fig. 2). It is interesting to note that the 2 patients requiring prolonged catheterisation (5 and 6 months) did not develop a stricture. The size of resectoscope sheath used showed no difference between the groups (Table 3). The weight of prostate resected is shown in Table 4. There was no significant difference between the groups. The histology, expressed as the percentage of benign glands, was also similar in each group.

The catheters used post-operatively were 22, 24 or 26 FG Simplastic or reinforced latex. Figure 3 shows the percentage of patients in each group in whom each size was used, and again there was no significant difference between the groups. The

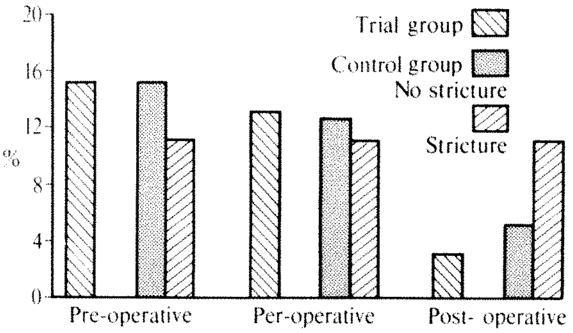

Fig. 1 Incidence of urinary tract infection.

Table 3 Resectoscope Used (Percentage Using 27 FG or 26 FG Sheath)

	Trial group (100)	*Control group (90)*
No stricture	84% (N = 84)	84% (N = 68)
Stricture	- (N = 0)	89% (N = 8)

Table 4 Weight of Prostate Resected (in grams)

	Trial group (100)	*Control group (90)*
	Mean SD (range)	*Mean SD (range)*
No stricture	14.8 ± 6.4 (4.0-48.0) (N = 100)	15.0 ± 6.0 (3.0-45.0) (N = 81)
Stricture	- (N = 0)	16.0 ± 4.5 (5.0-27.0) (N = 9)

duration of post-operative catheterisation was also very similar in each group (Fig. 4). It appears, therefore, that there was no difference between the groups apart from the pre-operative urethrotomy in the trial group.

Discussion

In 1963, Emmett *et al.* reported a series of 632 transurethral prostatectomies using preliminary urethrotomy: of those, 7 (1.2%) developed a stricture. This stricture rate was much lower than that of other published series and on this basis, many urologists use pre-operative urethrotomy routinely. However, Emmett's study was uncontrolled and we felt that a prospective controlled trial should be undertaken to confirm their findings. In our experience with urethrotomy, now extending to over 200 cases, the procedure has proved safe, simple and quick to perform. There have been no adverse effects reported in the literature. We have observed the urethra at the conclusion of resection in several patients and noted that the urethrotomy extends along the whole length of the urethra, except in some cases the bulbar urethra, the calibre of which is often greater than 30 FG. We did not urethroscope all our patients post-operatively as this would clearly be unethical, and therefore only those patients with symptoms suggestive of stricture were examined. Fourteen patients were urethroscoped, 12 from the control group, of whom 9 had strictures, and 2 from the trial group, neither of whom had a stricture. Whilst the stricture rate of 10% in the control group is well within the range of other published series, we were surprised that the number of strictures was so high. One reason for this may be that the majority of these cases required only 2 or 3 dilatations and these did not make a lasting impression on us. The impression made on the patient may, however, be rather more durable. It is clear that not all patients require a urethrotomy. If we could predict the

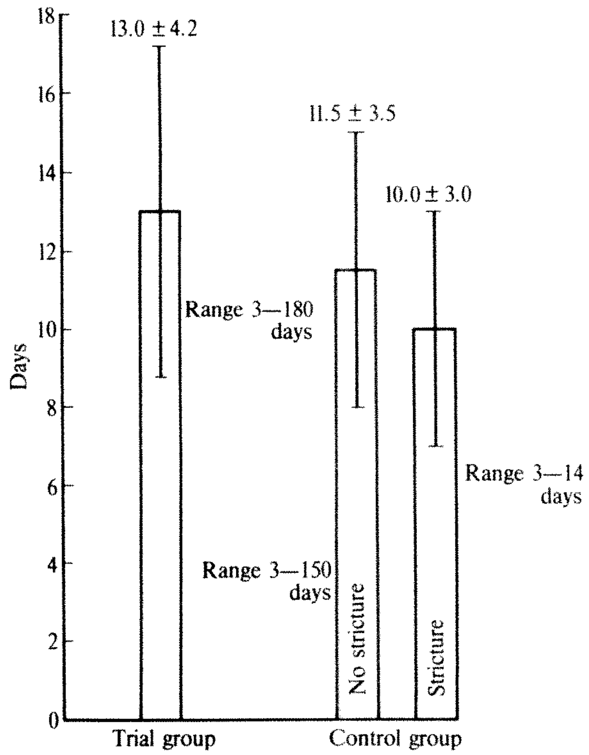

Fig. 2 Duration of pre-operative catheterisation.

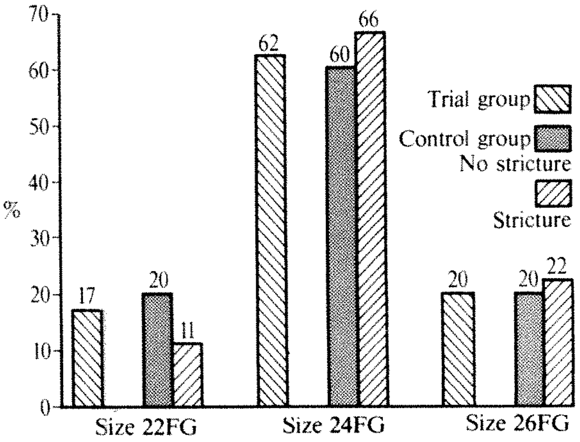

Fig. 3 Size of catheter used post-operatively.

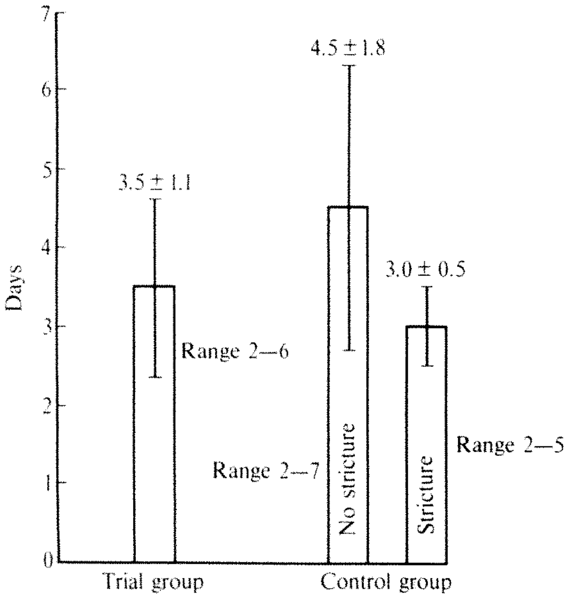

Fig. 4 Duration of post-operative catheterisation.

10% of patients at risk from stricture formation, the remaining 90% could be spared the procedure. However, we have been unable to identify any distinct difference between those patients who developed a stricture and those who did not.

It is concluded that internal urethrotomy using the Otis urethrotome calibrated to 30 FG significantly reduces the incidence of urethral stricture following transurethral prostatectomy, and the procedure is safe. It has not proved possible to predict which patients will develop a stricture, and we therefore believe that pre-operative full length urethrotomy should be performed in all patients about to undergo transurethral prostatectomy.

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Conservative Treatment of Carcinoma of the Penis

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Summary—Sixty-five cases referred to one hospital between 1964 and 1977 were studied. Forty-one presented in Stages 1 or 2 and when treated by the Iridium mould technique gave a 12/13 (92.3%) crude 5-year survival rate, an improvement over the results of previous methods of treatment, including partial amputation. In Stage 3 radical amputation gave an 89% 5-year survival rate.

Node dissection was reserved for inguinal nodes in Stages 1, 2 and 3 which failed to resolve after treating the primary tumour.

Undifferentiated tumours and those with the microscopic "cord" pattern of growth did badly.

Carcinoma of the penis is so uncommon in this country that significant advances in its treatment may easily go unnoticed. By tradition, this tumour has been treated by partial or total amputation of the penis, and block dissection of the regional lymph nodes when it is thought that they might be invaded by growth (Furlong and Uhle, 1953; Ekström and Edsmyr, 1958; Marcial *et al.*, 1962; Frew *et al.*, 1967; Edwards and Sawyers, 1968). However, Engelstad (1948) and Paterson (1963) showed that excellent control of the primary tumour could be obtained by local irradiation and over the last 15 years this has come to be the preferred method in use both in this hospital and elsewhere (Murrell and Williams, 1965; Jackson, 1966; Pointon, 1975; Orr *et al.*, 1977). Our approach has, however, differed from that used elsewhere. Initially we have aimed to be as conservative as possible, using at first radium, and latterly radioactive Iridium^{192} for the primary lesion. If the tumour was not amenable to Iridium mould treatment, or if it recurred, then we used an aggressive surgical excision. For the inguinal nodes treatment was deferred until the primary lesion had been dealt with. In this paper we present results which appear to support this policy.

Patients and Methods

Sixty-five consecutive unselected patients admitted to the London Hospital between 1964 and 1977 were studied. Their ages range from 34 to 83 years (Fig. 1). None of these patients was Jewish: 8 had been circumcised at intervals from 2 to 35 years before admission, but none of them in infancy. Two had a history of a previous chancre, 1 had documented treatment for venereal condylomata acuminata 4 years before, 1 had severe stenosing balanitis xerotica obliterans, 1 had had relapsing genital herpes for several years, and 19 complained of balanitis and phimosis. The histological diagnosis of the primary tumour had been made in other institutions before referral in 19 cases, but in 46 the original material could be re-examined for the purpose of histological grading. All cases have been followed up.

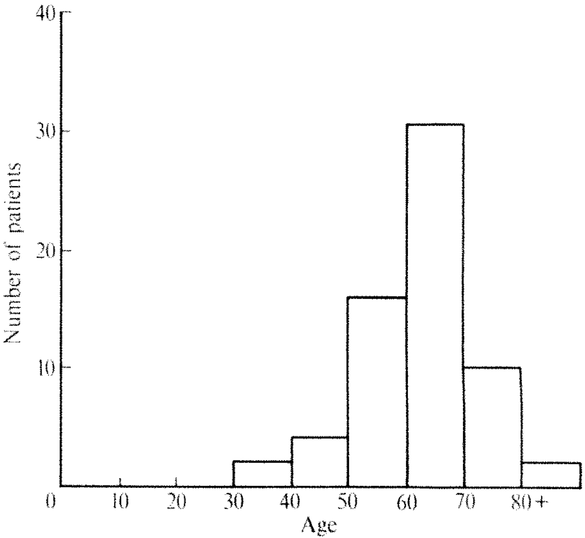

Fig. 1 Carcinoma of penis 1964 to 1977. Age at presentation in 65 patients.

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

Histological Grading

Histological material was examined by one observer (E.A.M.) who had no knowledge of the clinical details. Tumours were graded as well-differentiated, moderately differentiated and poorly differentiated (grades I, II, and III). In addition they were classified according to the 2 patterns of tumour growth described in detail by Frew *et al.* (1967). In this a distinction is drawn between the "solid" pattern, in which the tumour consists of relatively large rounded clumps and sheets, and the "cord" pattern, in which the tumour is composed of smaller cell masses, sometimes irregular in outline, and with intervening small clumps and slender cords of cells.

Clinical Staging

A modified version of the system of clinical staging proposed by Jackson (1966) was used. In Stage 1 are patients with tumours limited to the glans or prepuce. The TNM system subdivides these according to their maximum diameter, which we feel is less relevant than the "surgical" consideration of whether or not a partial amputation can easily be done, and, by the same token, an Iridium mould easily fitted. All of the Stage 1 cases would fall in T1 or T2. If there seems on palpation to be invasion of the shaft of the penis proximal to the glans, the case is placed in Stage 2, and would be T3 in the TNM system. The practical consideration here is that it is more difficult to fit an Iridium mould to the penis and yet ensure complete coverage of the growth, and if it came to partial amputation, there would be a temptation to perform too limited a removal of the growth. Stage 3 includes cases where the primary tumour is so big that no partial amputation can reasonably get clear of the growth, and no Iridium mould be safely fitted. These cases are included in T4. In Stage 4 the inguinal nodes are fixed and proved by biopsy to contain tumour, there are distant metastases, or the primary tumour is encroaching on to the abdominal wall or perineum: *i.e.* the case is inoperable by radical excision.

In this system, which differs only slightly from that of Jackson (1966) no attention is paid to the stage of the lymph nodes when the patient first presents, unless they are fixed, and biopsy confirms that they are invaded.

Methods of Treatment

The method of treatment which has been in use for the last 7 years has evolved slowly, and is now determined by the stage of the tumour at its presentation. It differs in 2 respects from that in common use elsewhere.

(1) Iridium mould treatment. Although in the early part of this series partial amputation was sometimes used, as well as radium, radioactive gold grains and tantalum wire for local treatment, and an external cobalt beam on one occasion, since 1970 the Iridium mould method has become the standard technique (Hope-Stone, 1975). First a biopsy of the tumour is obtained, and a formal complete circumcision performed: this step is essential and is combined with appropriate measures to control infection. An interval of about one week has usually passed before the paraffin section has been reported on, the circumcision is healing, and infection resolving. A plastic mould of cylindrical form is fitted to the penis, over which the patient is taught to slide an outer cylindrical applicator. When he has mastered this, and has been instructed how to note the duration of each application, the outside cylinder is armed with radioactive Iridium^{192} wire, its length measured so as to give a calculated dose of 6000 rads to the tumour, but only 5000 to the urethra. The applicator is removed by the patient when he wishes to urinate, and placed in a leaden safe beside the bed. The applicator is worn for 12 h a day for up to 7 days.

This technique has 3 chief advantages. First, there is no radioactive hazard to the nursing staff, since the patient puts on and takes off the applicator himself. Secondly, the Iridium wire is easy and safe to handle, the dose being readily and accurately calculated, with minimum irradiation hazard to the technician arming the applicator. Thirdly, the tumour gets the full dose of 6000 rads, but the urethra is spared, so reducing the threat of stricture.

Within 2 to 3 weeks there is a marked fibrinous reaction, which soon resolves with local steroid ointment and is healed within the month. Sexual intercourse is forbidden for 4 to 6 months.

(2) Radical amputation. For Stage 3 tumours where the original tumour has recurred, or is too large for the application of the Iridium mould, we have come to make use of an unusually radical amputation which is described in detail elsewhere (Blandy, 1976, 1978). Here the whole scrotal contents are removed, and a ∩-shaped flap let into the bulbar urethra so as to prevent stricture. The result is something resembling a vulva.

Management of the Inguinal Lymph Nodes

An inguinal node dissection was performed in men with Stage 1, 2 and 3 tumours, in whom the inguinal lymph nodes failed to resolve, or enlarged during the period of follow-up. Those with very large and advanced tumours in Stage 4 were treated with the utmost conservatism.

Results

Stage 1 (T1, T2; N0-2; M0)

Although in the early part of this series (Table 1 and Fig. 2), when most patients underwent partial amputation, there was a 77% 5-year survival rate, with Iridium mould treatment the survival had improved to 100%. One of the Iridium patients developed a local recurrence, underwent a partial amputation, and survived more than 5 years later. None of the Iridium group developed a stricture.

Stage 2 (T3; N0-2; M0) (Table 2)

Of the cases not treated by Iridium in the first instance 2 had local recurrences, one was amputated more proximally and another underwent a radical amputation. Only one died, after 4 years, with widespread metastases despite radiotherapy and bleomycin. Of those initially treated with the Iridium mould 2 developed recurrences and underwent partial amputation, and one died with metastases after 4 years.

Stage 3 (T4: N0-2: M0) (Table 3 and Fig. 3)

In those not treated by the radical amputation described here, there was an 80% 5-year survival. One patient was very fat, inoperable, and given external beam therapy. One died with carcinoma of the head of the pancreas. Of those treated by radical amputation 1 died with carcinoma of the lung. In 1 patient hard inguinal nodes were proved to be carcinomatous on biopsy, and he was treated with radiotherapy and bleomycin and is still alive at 5 years.

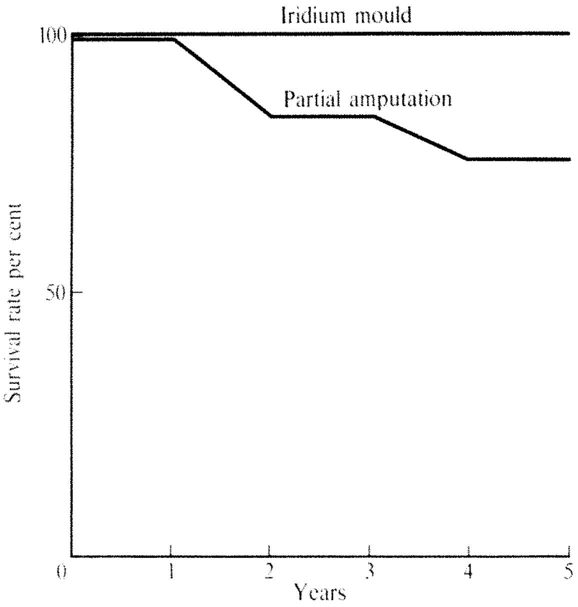

Fig. 2 Stage 1 carcinoma of penis: results.

Stage 4 (T4: N3: M0-1) (Table 4)

Only one patient has survived 3 years, after a combination of radical amputation, bleomycin and radiotherapy. One has died from carcinoma of the prostate, the remainder from distant metastases.

Management of the Inguinal Nodes

At the time of admission the inguinal lymph

Table 1 Stage 1 Carcinoma of the Penis

		Years				
		1	*2*	*3*	*4*	*5*
Partial amputation (13 cases)	Number	13	13	13	13	13
	Survived	13	11	11	10	10
	Crude survival rate (%)	100	85	85	77	77
Iridium mould (13 cases)	Number	12	10	9	9	8
	Survived	12	10	9	9	8
	Crude survival rate (%)	100	100	100	100	100
All methods of treatment (32 cases)	Number	29	28	28	28	27
	Survived	29	26	26	23	22
	Crude survival rate (%)	100	93	93	82	81

Table 2 Stage 2 Carcinoma of the Penis

		Years				
		1	*2*	*3*	*4*	*5*
Iridium mould (6 cases)	Number	6	6	5	5	5
	Survived	6	6	5	5	4
	Crude survival rate (%)	100	100	100	100	80
All methods of treatment (9 cases)	Number	9	8	7	6	6
	Survived	9	8	7	6	5
	Crude survival rate (%)	100	100	100	100	83

Table 3 Stage 3 Carcinoma of the Penis

		Years				
		1	*2*	*3*	*4*	*5*
Radical amputation (10 cases)	Number	10	9	9	9	9
	Survived	10	9	9	9	8
	Crude survival rate (%)	100	100	100	100	89
All cases (13 cases)	Number	13	12	12	10	10
	Survived	13	11	11	9	8
	Crude survival rate (%)	100	92	92	90	80

nodes were clinically enlarged in 43 out of the 65 cases (66%) In 11 of these clinical suspicion of malignancy was confirmed without delay by biopsy, placing the patient in Stage 4 with the results described above. Twenty were in Stage 1, of whom 17 are alive after more than 5 years: 1 was treated with partial amputation and Co^{60} and died at 3 years with cancer *en cuirasse*. In 3 patients the nodes recurred after treatment of the primary tumour, and node dissections were performed, removing positive nodes, at 2 and 3 years: all have survived 5 years. Five cases were in Stage 2; of these 4 are alive at 5 years, including 1 with a negative block dissection for clinically suspicious nodes, and 1 with biopsy proven nodes treated by radiotherapy and bleomycin who is still alive after 5 years. The fourth patient is alive at 3 years. In the Stage 3 group 7 had enlarged nodes: one aged 80 was unfit for amputation and died before he could complete a course of radiotherapy: the remainder are alive at 2, 3, and 5 years.

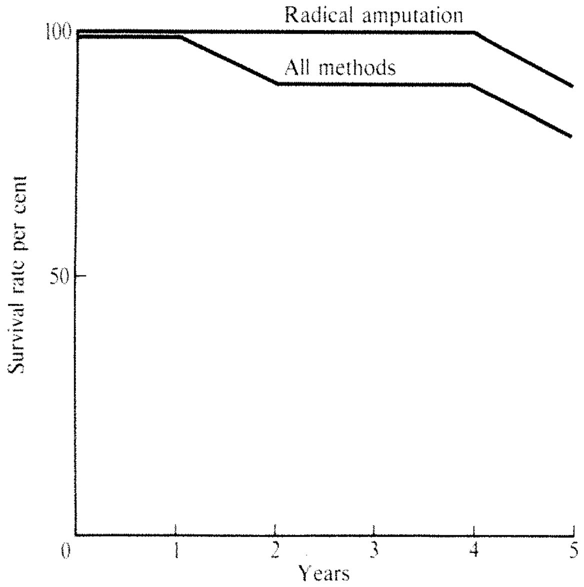

Fig. 3 Stage 3 carcinoma of penis: results.

Survival and Histological Features

There was a very close correlation between the histological grade and the survival rate, as well as with the proportion of patients in each group presenting in the more advanced stages (Table 5). There was also a very striking relationship between the pattern of tumour growth and the prognosis. The well-differentiated tumours with the solid pattern had a 100% 5-year survival rate: in contrast, those with the cord pattern, whose tumours were other than well-differentiated, had only a 45% 5-year survival.

Table 4 Stage 4 Carcinoma of the Penis

		Years				
		1	*2*	*3*	*4*	*5*
All cases (11 cases)	Number	11	11	9	8	6
	Survived	9	2	1	0	0
	Crude survival rate (%)	82	18	11	0	0

Discussion

The obvious advantage to the patient, who is spared an amputation, is justified when the long-term results of Iridium mould treatment in Stages 1 and 2 are evaluated. Overall there was a 12/13 (92.3%) crude survival rate in this group. It may be relevant that among the entire group of 19 men treated initially by Iridium moulds in Stages 1 and 2, only one developed inguinal metastases (5%) in contrast to the 22 treated by partial amputation and other techniques, in whom 4 (18%) developed inguinal metastases. It seems possible that even in cases where amputation has been decided upon, there may be good reason to begin with a pre-operative course of radiotherapy.

In the more advanced cases (Stage 3) radical amputation seems justified by the 89% crude survival rate noted here, and the entire absence of post-amputation urethral stricture. In this ageing population other factors reduce the survival rate, and it is of interest that in 8 of these patients there were no less than 10 other primary neoplasms (4 in the lung, and one each in pancreas, stomach, pituitary, bladder and bone, and one lymphoma).

Inguinal node dissection was reserved for patients whose nodes failed to resolve or recurred after the primary tumour had been treated, and in this group the results seem justified. Routine radical inguinal node dissection in the early stages of carcinoma of the penis can hardly be condoned, and in the late stages seems to be entirely futile. This may be related to the finding that in these more advanced cases the histological features of the tumour are much more aggressive, as was noted by Frew *et al.* (1967), and it would seem more logical to seek better cancer chemotherapy than to extend the scope of node dissection.

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Table 5 Survival and Histological Differentiation of the Primary Tumour

Histological grade	*5-year crude survival rate*			*Stage at admission*			
	No.	*Survived*	*5 year s.r.*	*Stage 1*	*Stage 2*	*Stage 3*	*Stage 4*
I Well differentiated (22)	17	16	94%	13 59.1%	7 31.8%	2 9.1%	0 0%
II Moderately differentiated (14)	8	6	75%	9 64.3%	1 7.1%	3 21.5%	1 7.1%
III Poorly differentiated (10)	7	2	29%	2 20%	0 0%	0 0%	8 80%
Pattern of tumour growth Solid (19)	16	15	94%	12 63.2%	5 26.3%	2 10.5%	0 0%
Cords (27)	14	9	64%	12 44.5%	3 11.1%	3 11.1%	9 33.3%

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Releasing Factor Tests in Men with Oligozoospermia

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Summary—FSH levels were assayed in 300 men attending with infertile marriages. From this number, releasing factor tests were carried out in 24 men with oligozoospermia and an initial FSH below our normal mean. In all of these cases there was a response to releasing factor. Isolated FSH deficiency is likely to be rare in adult men presenting with infertility and no previous endocrinological history.

Several studies have demonstrated that elevated follicle stimulating hormone (FSH) levels correlate with testicular abnormality and falling sperm density (Franchimont *et al.*, 1972) and our own work supports this (Hargreave *et al.*, 1977; Hargreave and Jequier, 1978). A group of oligozoospermic men emerge from our studies who may have inappropriately low FSH levels. Because our FSH radioimmunoassay is insensitive at the lower limit of our normal range it is difficult to distinguish men with an abnormally low FSH from normal cases. This study was undertaken to try to detect cases of pituitary gonadotrophin insufficiency in men with oligozoospermia and an initial low FSH.

Patients and Methods

FSH levels were assayed in 300 men attending the infertility clinic at the Western Infirmary, Glasgow. Following their visit semen samples were obtained and those with a sperm density of less than 60 million/ml had further samples examined. All semen samples were collected after 3 days' avoidance of intercourse. The sperm density recorded in this paper is the best individual attained, not the average. Oligozoospermia is defined as a density of less than 40 million/ml. Our normal FSH range is 3.07 + 1.8 u/l (Hargreave *et al.*, 1977).

Table 1 Sperm Density and Initial FSH Levels in Men Tested with Releasing Factor

Sperm Density millions/ml	*No. of Men*	*Initial FSH* *<3.07*	 *>3.07*
Azoospermic	4	2	2
<5	5	3	2
5–9	5	5	
10–19	6	6	
20–39	10	10	
40–60	8	8	
>60	2 Fertile		

From the 300 men we offered releasing factor tests to all those with an initial FSH of less than 3.07 u/l and sperm density below 60 million/ml (Table 1). Men with varicoceles were excluded. Two men with recently proven fertility, normal physical examination and sperm density above 60 million/ml also agreed to be tested. In addition we report the results of releasing factor tests in 4 azoospermic men and 2 men with low sperm density but an initial high FSH (Table 1).

A basal blood sample was taken and then 100 μg of synthetic hypothalamic releasing factor (Ayerst Laboratories) was given slowly intravenously. Blood samples were taken at 15, 30, 60, 90, 120 and 180 min after injection. All specimens were separated immediately and the plasma stored at −20°C prior to analysis. FSH and luteinising hormone (LH) were measured by radioimmunoassay using a double antibody precipitation method. The LH assay used an antiserum raised to human chorionic gonadotrophin and reference standard was obtained from the Medical Research Council (68/69). The FSH antiserum was raised against human FSH and was obtained from Professor W. F. Butt and the reference preparation was MRC 69/104.

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

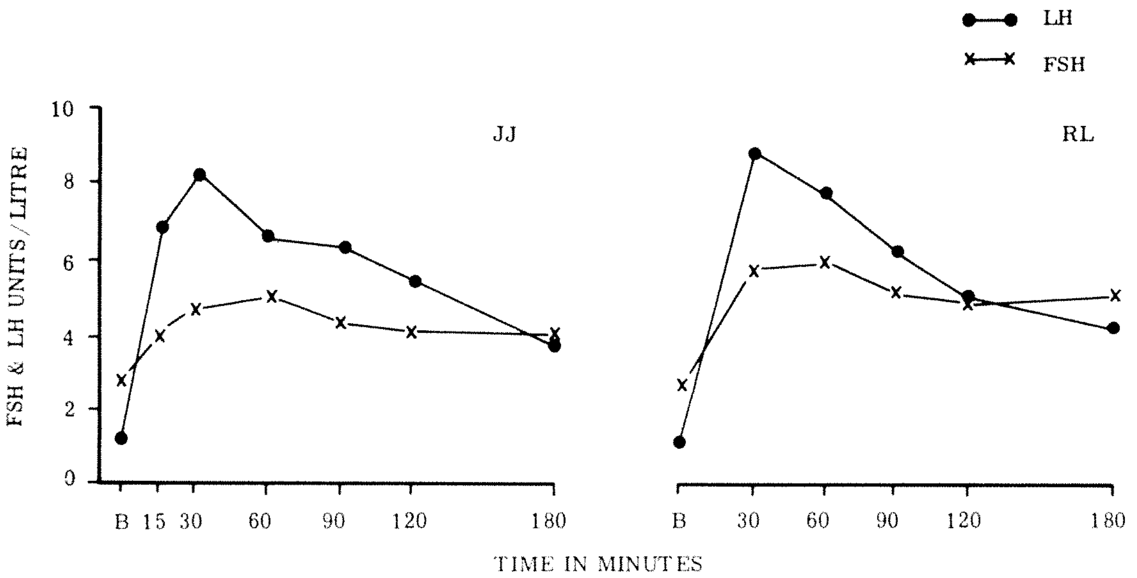

Fig. 1 FSH and LH response: 2 fertile men (JJ and RL).

Results

The FSH and LH response in the 2 control subjects are shown in Figure 1.

The FSH responses in the 32 men with an initial FSH of <3.07 u/l and the 2 control subjects are shown in Figure 2 and Table 2. There appears to be a flattening of response with increasing sperm density which was also noted with the LH response (Table 3). However, statistical analysis reveals no difference in the degree of response in any of the groups.

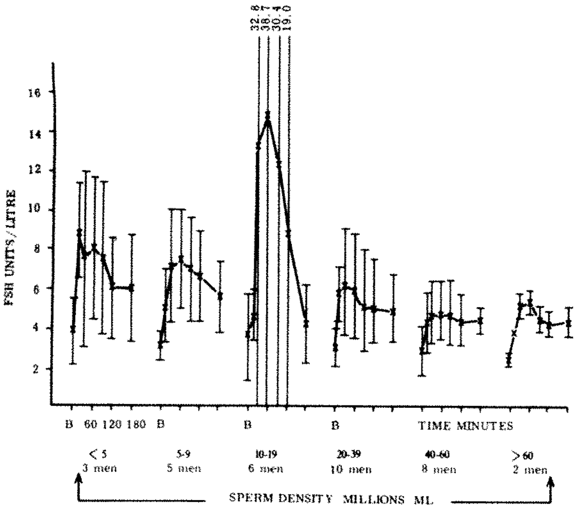

Fig. 2 FSH response: 32 men with initial FSH <3.07 u/l.

The 10–20 group contains one man with an exaggerated response (Fig. 3). It is also apparent from Figure 3 that the variation in the response in patients within a group can be marked but the FSH response parallels the LH response in degree and this was noted throughout the study.

Two men were tested who had a high initial FSH, both with a sperm density of less than 5 million/ml (Fig. 4). It is of interest that case J. B., despite a high initial FSH (13.0 u/l) and a marked LH response, had a relatively flat FSH response. This was the only case seen where the LH response did not parallel the FSH response.

Four azoospermic men were also tested (Fig. 5). One of these (R.O.) was clinically androgen deficient, had a flat response and has been started on replacement therapy. Another man with Sertoli cells only (J.McC.) had a delayed rise in FSH. It seems unlikely that replacement therapy in his case will cause regeneration of germinal epithelium and he has declined further investigation.

Discussion

The results show that all of the patients with an initial FSH of less than our normal mean had a response to releasing factor. This makes it improbable that isolated FSH deficiency is a common

Table 2 FSH Response to Releasing Factor in 34 Men with an Initial FSH of Less than 3.07

Sperm Density (m/ml)	*No. of Men*	*Basal*	*15*	*30*	*60*	*90*	*120*	*180*
<5	3	3.8 ± 1.73	8.85 ± 2.47	7.53 ± 4.55	8.03 ± 3.66	7.50 ± 3.92	5.97 ± 2.68	6.03 ± 2.76
5–9	5	3.10 ± 0.83	5.13 ± 1.96	7.18 ± 2.95	7.56 ± 2.52	7.06 ± 2.74	6.70 ± 2.37	5.62 ± 1.83
10–19	6	3.58 ± 2.32	4.66 ± 1.38	13.22 ± 19.58	14.95 ± 23.76	12.33 ± 18.08	8.73 ± 10.29	4.12 ± 2.10
20–39	10	3.08 ± 1.09	5.83 ± 1.47	6.34 ± 2.82	6.23 ± 2.70	5.55 ± 2.68	5.43 ± 2.22	5.05 ± 1.76
40–60	8	2.85 ± 1.31	4.32 ± 1.63	4.85 ± 1.67	5.0 ± 1.57	4.81 ± 1.72	4.50 ± 1.44	4.45 ± 0.70
>60	2	2.40 ± 0.14		5.15 ± 0.78	5.45 ± 0.64	4.60 ± 0.71	4.35 ± 0.64	4.40 ± 0.85

Table 3 LH Response to Releasing Factor in 34 Men with an Initial FSH of Less than 3.07

Sperm Density (m/ml)	*No. of Men*	*Basal*	*15*	*30*	*60*	*90*	*120*	*180*
<5	3	3.13 ± 0.81	12.9	12.83 ± 3.51	11.50 ± 3.28	9.23 ± 2.41	7.70 ± 2.46	6.03 ± 2.19
5–9	5	2.22 ± 0.89	11.03 ± 4.21	14.72 ± 3.76	11.80 ± 2.96	9.34 ± 1.89	7.64 ± 1.46	5.60 ± 0.86
10–19	6	1.72 ± 0.83	8.98 ± 2.60	14.9 ± 10.3	12.7 ± 7.59	9.75 ± 5.66	6.98 ± 2.9	4.38 ± 1.19
20–39	10	2.53 ± 1.19	14.06 ± 11.41	15.91 ± 14.06	13.50 ± 10.6	9.91 ± 7.15	8.3 ± 5.39	6.09 ± 3.16
40–60	8	2.31 ± 0.68	8.02 ± 1.99	10.34 ± 4.26	9.06 ± 3.05	7.84 ± 2.6	6.5 ± 2.11	4.64 ± 1.06
>60	2	1.00 ± 0.00	6.7	8.55 ± 0.49	7.15 ± 0.92	6.25 ± 0.07	5.15 ± 0.35	3.90 ± 0.28

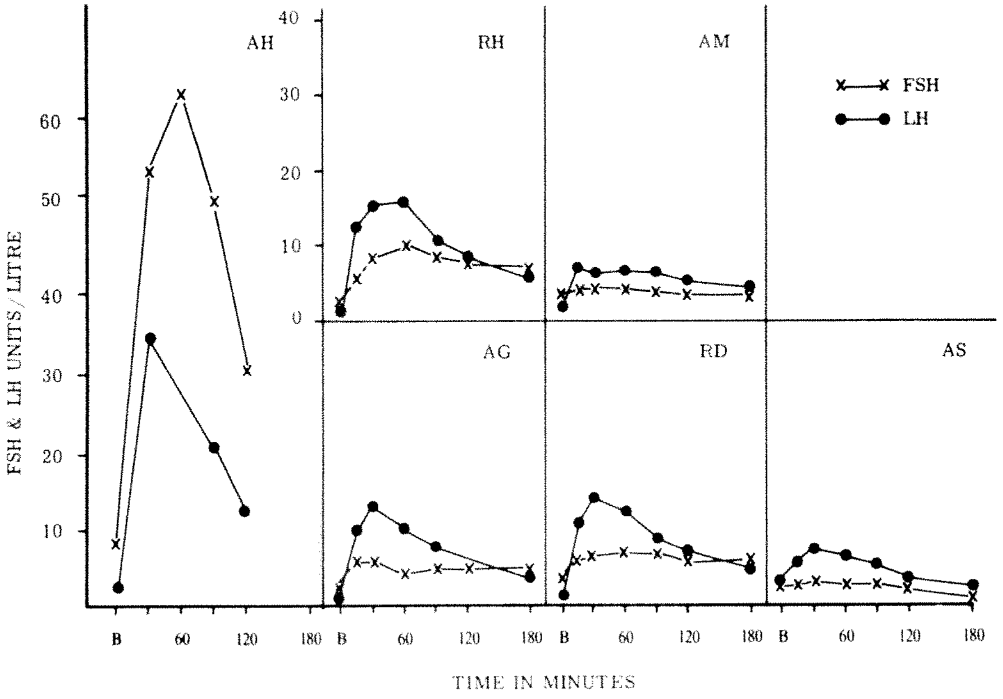

Fig. 3 FSH and LH response: 5 men with sperm density between 10 and 20 million/ml and initial FSH <3.07 u/l.

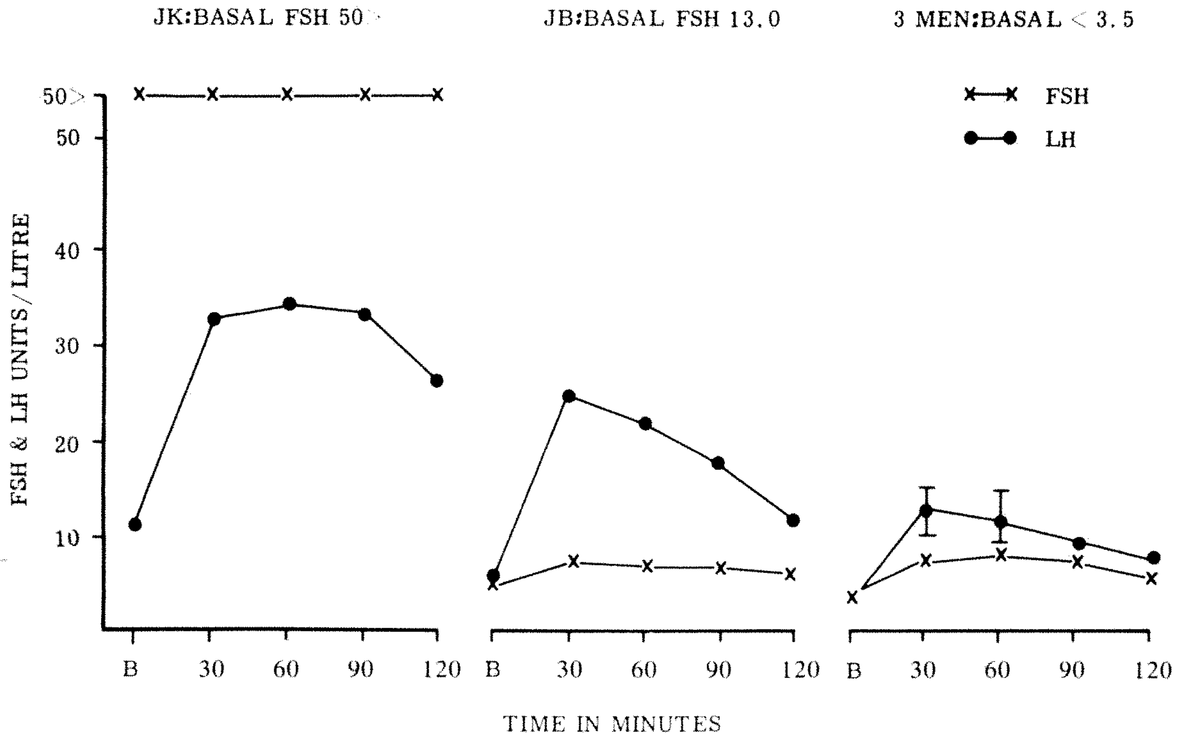

Fig. 4 FSH and LH response: 5 men with sperm density below 5 million.

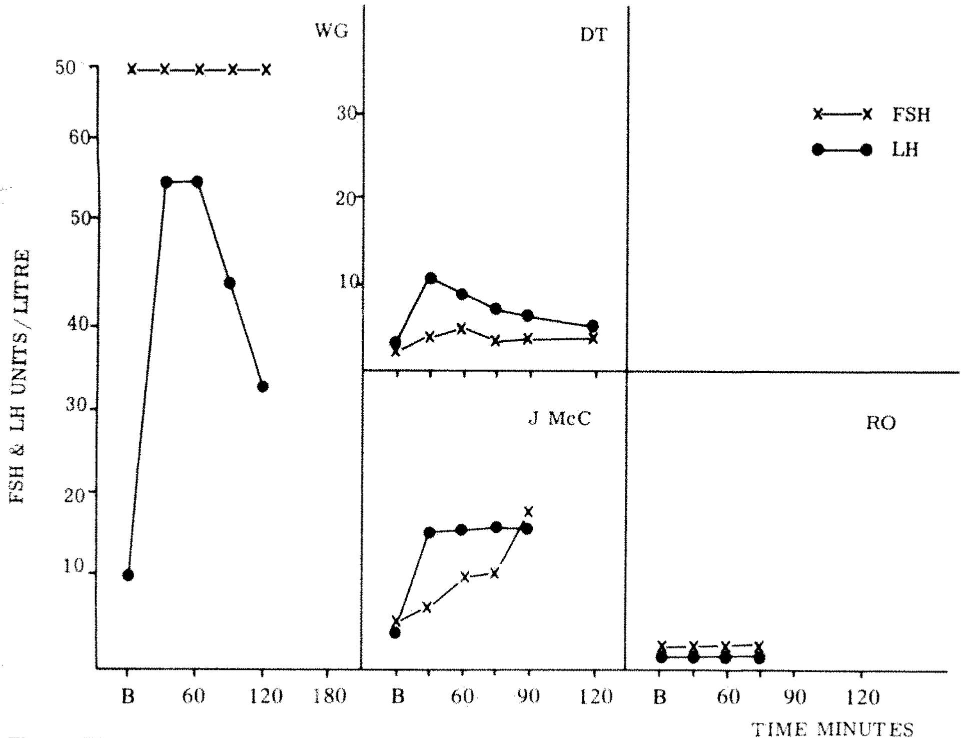

Fig. 5 FSH and LH response: 4 men with azoospermia.

cause of oligozoospermia or that replacement therapy will help. These results suggest that treatment of oligozoospermic men with FSH replacement in most cases will be attempts to manipulate a normal hormonal state.

The apparent flattening of FSH and LH response as the sperm density increases is not confirmed on statistical analysis. There were greater variations about the mean in the low density groups and it seems that in these groups there may be a number of men with exaggerated responses. We have probably selected against men with exaggerated responses who might be expected to have had a higher basal FSH and we have seen only one case (A. H., Fig. 3).

Previous reports of FSH and LH deficiency (Marshall *et al.*, 1972) are usually concerned with young adults who fail to mature properly. The occasional case may arrive in the infertility clinic (*e.g.* R.O., Fig. 5) but this man had received previous androgen therapy and as a rule androgen deficiency and late epiphyseal closure lead to an earlier diagnosis. Thus previously unsuspected cases are likely to be pure FSH deficiency. Our study would indicate this is rare in a general male infertility clinic. It is interesting to note case J.B. (Fig. 4) where the FSH response was poor compared with exaggerated LH response. There may be a condition where the pituitary is capable only of partial FSH response. This man appeared sensitive to the given dose of releasing factor as evidenced by the good LH response. A wide discrepancy between LH and FSH response may be an indication for replacement therapy.

At the present time we do not recommend using releasing factor tests except when clinically indicated. Examples are men with other pituitary problems, men with androgen deficiency and late epiphyseal closure and men with reduced Leydig cell population on testicular biopsy associated with a sparse germinal epithelium. Sampling can reasonably be carried out at 30, 60 and 90 min after injection.

This work forms part of a thesis to be submitted for the Degree of MS, London University, by T. B. Hargreave.

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Experience with Vasovasostomy: Operative Technique and Results

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Summary—Between 1972 and 1977 vasovasostomy to reverse a previous vasectomy for contraception has been attempted in 27 cases. The procedure was abandoned as a technical impossibility in only 1 case.

The first 17 have been studied and in these there have been 11 pregnancies, 10 of which have already come to term with the birth of normal children, including one set of twins. Of the remainder, 2 are known to have oligozoospermia and 4 have been lost to follow-up although 2 of these were euspermic when last heard of.

In spite of the encouraging results it is considered that there are no grounds for altering the present basis of vasectomy counselling in which the operation is described as likely to be irreversible.

With vasectomy increasing in popularity as a means of contraception, and now available within the National Health Service, it is anticipated that an increasing number of men will request a reversal procedure. In the United States 6.7% of vasectomised men have subsequently sought re-anastomosis (Davis and Hulka, 1970).

There is, however, a disparity between the rate of technical success of vasovasostomy (the restoration of normal values on seminal analysis) and the rate of functional success (the occurrence of pregnancy). Although the rates of technical success vary between 38% (Derrick *et al.*, 1973) and 90% (Silber *et al.*, 1977), the rates of functional success vary between 18.6% (Dorsey, 1973) and 59% (Silber *et al.*, 1977).

Mechanical (Silber *et al.*, 1977), hormonal (Smith *et al.*, 1976; Kinson *et al.*, 1977) and immunological (Ansbacher *et al.*, 1972) causes for this disparity have all been postulated.

Patients and Methods

A total of 27 operations for reversal of vasectomy has been undertaken since June 1972. The first 17 have been taken as the review group in respect of the rate of functional success as 18 months or more have elapsed from the time of vasovasostomy.

The youngest at the time of vasectomy was 28 years and the oldest 45 years, average 32.3 years (Table 1). The youngest at the time of vasovasostomy was 30 years and the oldest 49 years, average 36.1 years. The interval between vasectomy and vasovasostomy varied from 7 to 120 months, average 46.4 months.

Of the 27 reversals undertaken, 21 were done for divorce and remarriage, 3 following the death of an existing child or children, and 1 for a change of mind. The indication was not known in 2 cases.

All patients were followed for evidence of both technical and functional success.

Vasovasostomy

Under general anaesthesia, separate right and left transverse scrotal incisions were made, the testis being delivered within the tunica vaginalis. The tunica was opened only sufficiently to remove a small sample of testicular tissue for histological examination and the wounds in the tunica albuginea and the tunica vaginalis separately closed. Thereafter, the vasectomy site was explored and the proximal and distal ends defined and held with stay sutures through the adventitia. Complete

Table 1 Age at Vasectomy and Vasovasostomy, and Duration of Vasectomy

Age at vasectomy (years)	*Age at reversal (years)*	*Duration of vasectomy (months)*
28-45 (32.3)	30-49 (36.1)	7-120 (46.4)

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

separation of the tied ends of the vas was uncommon. Usually there was a fibrous band between the ends and sometimes actual union with an intervening nodule of dense scar tissue. The section with the obliterated lumen was excised to expose patent proximal and distal vas. In 2 cases in which there had been a previous attempt at vasovasostomy elsewhere the scarring was considerable. In some, where the site of vasectomy had been near the epididymis, the proximal remnant was the convoluted portion of the vas, which increased the difficulty of the anastomosis.

At this stage the epididymis was massaged from head to tail until epididymal fluid appeared in the lumen of the proximal end. This both confirmed the patency and allowed a sample to be taken for microscopic examination.

A 21 gauge hypodermic needle from which the tip had been honed was passed down the lumen of the proximal vas for a distance of 0.5 cm or further in the direction of the epididymis and then through the vas wall (Fig.). Through this, a length of No. 1 monofilament nylon was passed and retrieved from the butt end. The needle was withdrawn, leaving the nylon *in situ*. This nylon splint was then passed down the lumen of the distal vas as far as it would go, usually 18 to 20 cm. This gave an indication of the integrity of the distal lumen beyond the vasectomy site. Dexon 3/0 on a taper pointed atraumatic needle was used to approximate the 2 ends of the vas, picking up only the adventitia and outer muscular layer and avoiding the lumen. Four interrupted sutures were used and care was taken at the time of tying to ensure only enough tension to create a firm knot without pulling the suture through the vas wall. Several additional anchoring sutures were used to approximate the surrounding tissues and to take any strain from the anastomosis. The nylon splint was brought out through the scrotal wall above the incision and fixed to the skin.

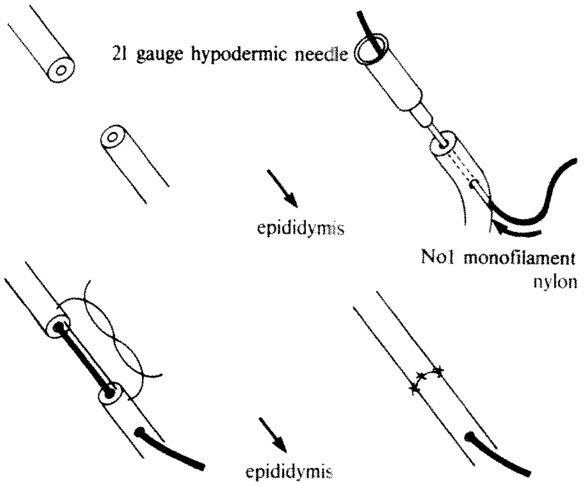

Fig. Vasovasostomy: operative procedure.

The monofilament nylon splint was removed on the fifth post-operative day and strict bed-rest maintained until the seventh to reduce the chance of distraction or tension on the anastomosis and the risk of disruption and scarring. The patient was also advised to wear a scrotal support for 2 to 3 weeks after ambulation.

Results

Of the 27 cases of vasovasostomy undertaken the only complication occurred in the first case, in which a vasogram had been performed on one side. A mild epididymitis on this side resolved spontaneously. Vasography was not performed in subsequent cases.

The first 17 cases constitute the review group. Of the remaining 10 cases one was abandoned when it was found that on each side the vasectomy site involved the lower pole of the epididymis and there was gross scarring. The other 9 are being followed up.

Seminal analysis has been undertaken 2 months post-operatively and at various times thereafter. Initially the counts have usually been low in density (5 to 10 million/ml) with some impairment of motility. Subsequent specimens have shown progressive improvement in sperm density, viability and motility, except in 2 cases in which oligozoospermia has persisted. The interval between vasectomy and reversal in one of these was 10 years; the other had considerable scarring due to a previous attempt at vasovasostomy and was subsequently found to have active pulmonary tuberculosis and is currently on antituberculous chemotherapy.

Of the 17 cases in the review group there have been 11 pregnancies (64.7%). Ten of these have gone to term with the delivery of normal healthy infants, including one set of twins. One pregnancy continues without complication. Of the remaining 6, 2 continue under surveillance with oligozoospermia and 4 have been lost to follow-up, although 2 of these were known to have normal seminal analyses when last heard of. The interval between vasectomy and vasovasostomy in the 11

Table 2 Duration of Vasectomy in Review Series and in Cases Reponsible for Production of Pregnancies

	All review cases (17)	*Cases responsible for subsequent pregnancies* (11)
Duration of vasectomy (months)	7-120 (46.4)	7-72 (39.8)
Conception time (months)	-	5-24 (10.4)

functionally successful cases ranged between 7 and 72 months, average 39.8 months (Table 2). The interval between vasovasostomy and conception has been 5 to 24 months, average 10.4 months.

Discussion

Although the operation requires a careful technique it is not difficult and can be adequately accomplished with conventional surgical methods. This is contrary to the opinion of some (Silber *et al.*, 1977), who consider microsurgical techniques essential to achieve functional success.

The choice between conventional and microsurgical method is optional, but if standard measures are undertaken it is considered important to splint the lumen of the vas with monofilament nylon, to support the anastomosis by anchoring stitches through the tissue around the vas, and to maintain post-operative bed-rest. It has been demonstrated in experimental work in rats (Hagan and Coffey, 1977) that escape of sperm into the anastomosis or its surrounding tissue results in gross scarring, while a patent anastomosis with a minimum of scarring occurs in more than 85% when spermatozoa are excluded from the area of healing either by mechanical means or by temporary suppression of spermatogenesis.

In accounting for the high success rate in the present series it is considered that the enforced bed-rest is important to minimise the strain on the anastomosis and the risk of sperm leakage into the surrounding tissue. The use of the monofilament nylon splint together with milking the epididymis of sperms at the time of operation may also reduce the chance of anastomotic sperm leak in the immediate post-operative period.

Although the rate of functional success in the review group of this series is encouraging and suggests a reasonable chance of return to fertility after vasovasostomy, there are no grounds for altering the basis of vasectomy counselling in which applicants are asked to accept that the operation may not subsequently be reversible.

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British Journal of Urology (1979), **51**, 46

Case Reports

Leiomyosarcoma of the Penis

Case Report

A 60-year-old Zambian male presented with a 1 month history of a painful swelling of the penis. Physical examination showed a firm tubular swelling along the penile urethra. The overlying skin was freely mobile. Regional lymph nodes were not enlarged. A chest X-ray was normal. The mass and the spongy urethra were excised. The tumour (Fig. 1) originated from the entire length of the corpus spongiosum. The cavernous tissue was not involved. A histological diagnosis of poorly differentiated leiomyosarcoma (Fig. 2) was made. The patient died 4 weeks later and post-mortem examination showed metastases to the deep inguinal nodes, pelvic nodes and both lungs.

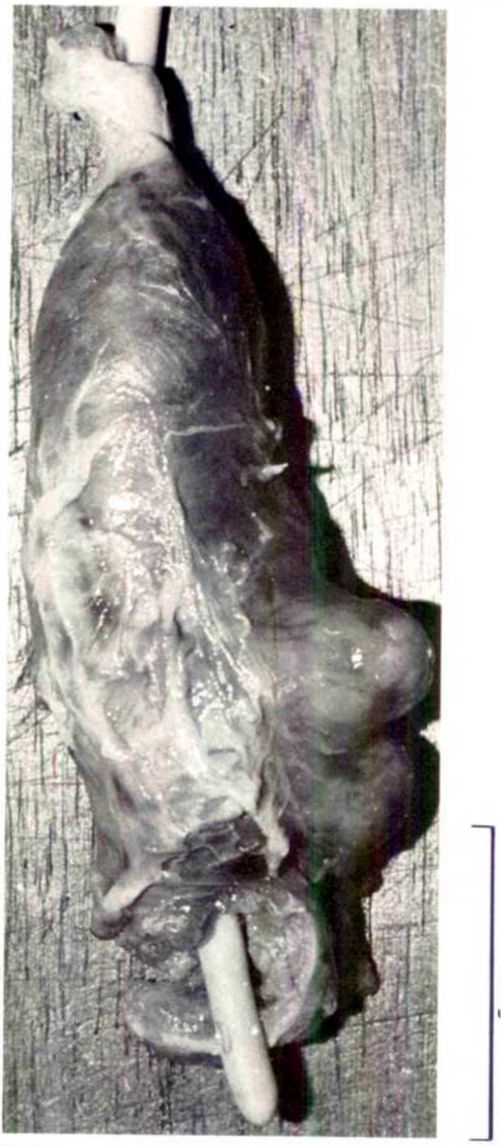

Fig. 1

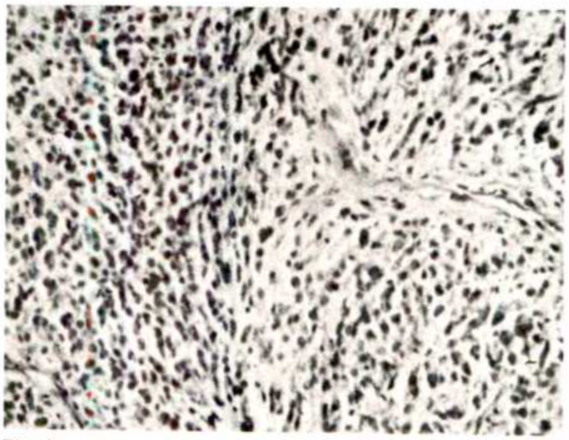

Fig. 2

Comment

Leiomyosarcoma of the penis is rare. Only 11 cases have been described in the English literature (Hamal, 1975). McKenzie Pratt and Ross (1969) divided such tumours into 2 groups according to the site of origin. This case appears to belong to the second group but demonstrates some unusual features. Origin of the tumour from the corpus spongiosum and metastasis to the deep inguinal nodes have not been previously reported. Wide dissemination of the tumour soon after surgery with early death has been observed in only 1 case (Bakken *et al.*, 1968). Leiomyosarcoma of the penis usually carries a better prognosis, and widespread metastasis with early death may be a feature of the highly anaplastic type of tumour.

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British Journal of Urology (1979), **51**, 47

Massive Pelvic Arteriovenous Fistula

Case Report

A 37-year-old female presented with symptoms of lower abdominal discomfort and was found on pelvic examination to have a discernible soft right pelvic mass with palpable thrill. Urinalysis showed occasional red blood cells and intravenous pyelogram showed displacement of the bladder to the left with ureteric deviation. Cystoscopy revealed displacement of the right bladder wall by an extrinsic mass with dilated veins coursing along the lateral edge of the bladder, but without any mucosal abnormalities. Aortogram revealed a massive pelvic arteriovenous fistula whose arterial origin was the internal iliac artery (Fig.). The patient's past history was unremarkable except for a tubal ligation performed 13 years previously. The fistula was explored transabdominally and the predominant feature of the mass was multiple dilated veins. The internal iliac artery and all feeding vessels and fistulous connections were removed and follow-up arteriogram showed no further evidence of arteriovenous connections.

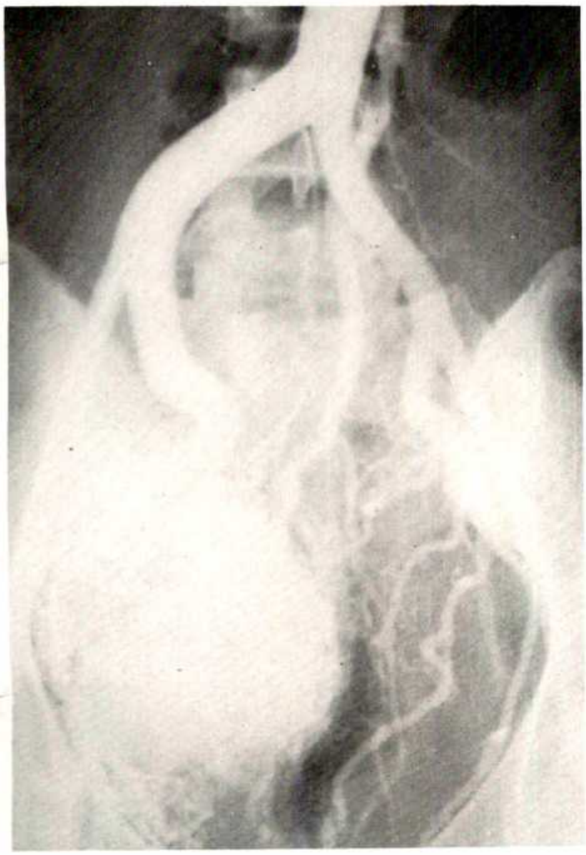

Fig.

Comment

Arteriovenous fistulas in the pelvis, congenital or traumatic, are quite rare (Spencer, 1969). Penetrating injuries of the pelvis would be the most common cause of this type of fistula. Penetrating iatrogenic trauma must also be considered within this context. This patient's fistula was most likely congenital in origin but in view of her tubal ligation, an iatrogenic source cannot be excluded.

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Secondary Prostatic Tumour of the Spermatic Cord and Epididymis 5 Years After Prostatectomy and Vasectomy

Case Report

A.M., a 70-year-old man, presented with an adenocarcinoma of the prostatic remnant 5 years after retropubic prostatectomy and bilateral vasectomy for benign prostatic hypertrophy. He was treated by bilateral orchidectomy and at this operation a hard discrete white nodule, 1 cm in diameter, was found adherent to the right epididymis and cord about 2.5 cm distal to the cut end.

Section of the nodule revealed an adenocarcinoma, similar in appearance to that of the prostatic biopsy, infiltrating the wall of the epididymis and the vas deferens (Fig. 1). The lumina of the vas, epididymis, lymphatic and blood vessels were free of tumour. Perineural involvement within the tumour (Fig. 2) was striking but was not seen in the proximal cord at the level of transection.

Comment

Carcinoma of the prostate rarely spreads to the epididymis (Wachtel and Mehan, 1970). In our case we cannot demonstrate any of the 4 modes of spread (arterial, venous, lymphatic and intraluminal) proposed by Wolf and Madson (1968). Spread through the interstitial tissue of the perineurium and epineurium (Willis, 1973) within the tumour must have occurred after the development of the metastasis because it was not found at the level of transection. As there is no recurrence in the scar 8 months after orchidectomy, direct spread from the prostate is unlikely. The most likely mode of spread is by arterial, venous or lymphatic embolisation from occult metastatic carcinoma elsewhere in the body, although there is no positive evidence for this in the sections examined.

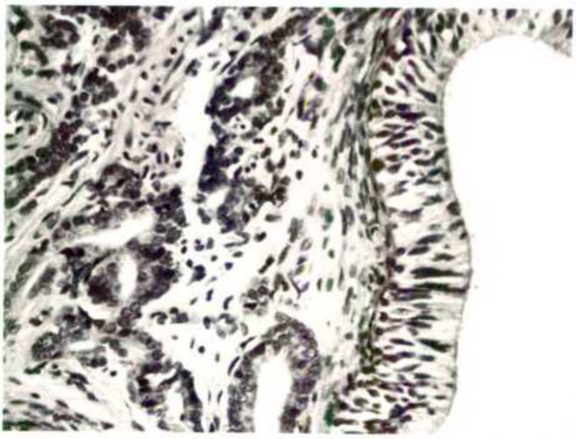

Fig. 1 Section of nodule from epididymis and cord (× 160).

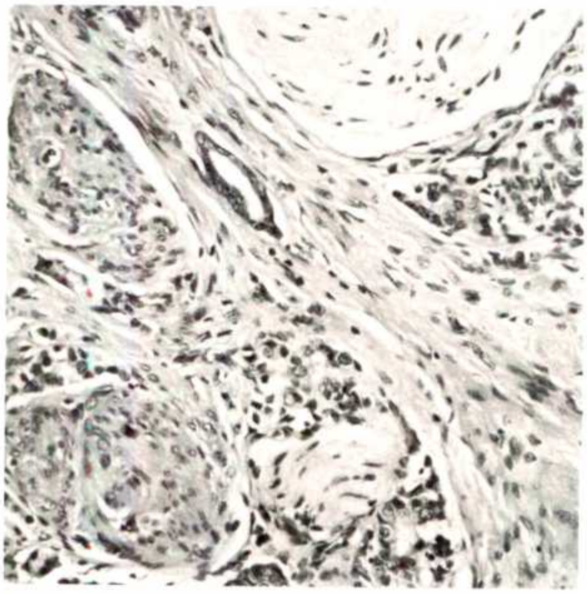

Fig. 2 Section of nodule from epididymis and cord showing perineural involvement (× 160).

Acknowledgement

We thank Mr P. F. Philip, Charing Cross Hospital, for permission to present the case of a patient under his care.

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British Journal of Urology (1979), **51**, 49

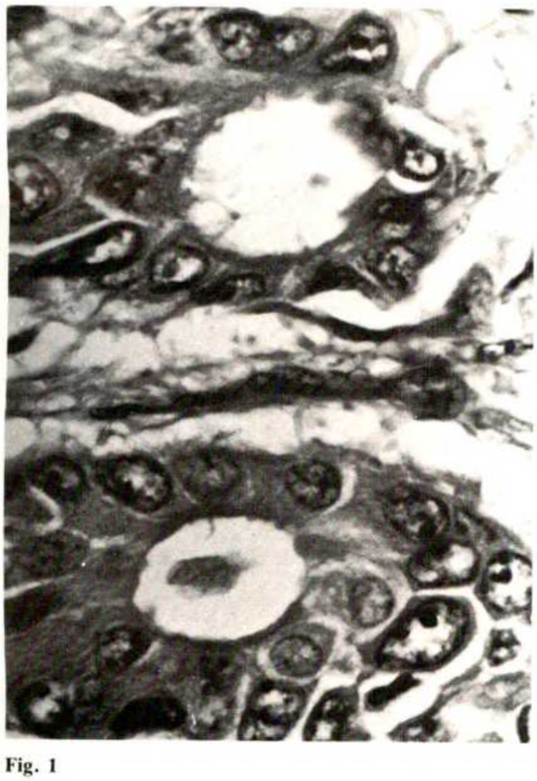
Simultaneous Prostatic Carcinoma and Genital Paget's Disease Associated with Subjacent Adenocarcinoma

Case Report

In April 1976 a 65-year-old Japanese male presented with a 3 year history of a treatment-resistant erythematous lesion of the scrotal skin and a 1 year history of painful, frequent and incomplete urination. Examination revealed both prostatic carcinoma and extramammary Paget's disease of scrotal skin. In the dermis of the scrotum underneath the Paget's cells in the epidermis were nests of adenocarcinoma, the cells of which were eosinophilic and had abundant cytoplasm, round, elliptical or reticulate nuclei and clear nucleoli (Fig. 1). The cells of the prostatic carcinoma were generally small with sparse cytoplasm and indistinct nucleoli (Fig. 2). The cells of the Paget's disease and of the subjacent adenocarcinoma stained positive with PAS before and after diastase, with Alcian blue, with mucicarmine and with toluidine blue at pH 4.2, whereas the cells of the prostatic carcinoma did not.

Comment

Grimes (1959) and Ikezawa *et al.* (1977) reported extramammary Paget's disease associated with prostatic carcinoma. This patient had extramammary Paget's disease associated with subjacent adenocarcinoma and prostatic carcinoma. As histochemical and morphological studies confirmed that the former disease was different from the latter, this case satisfies the definition of multiple primary cancers given by Waren and Gates (1932).



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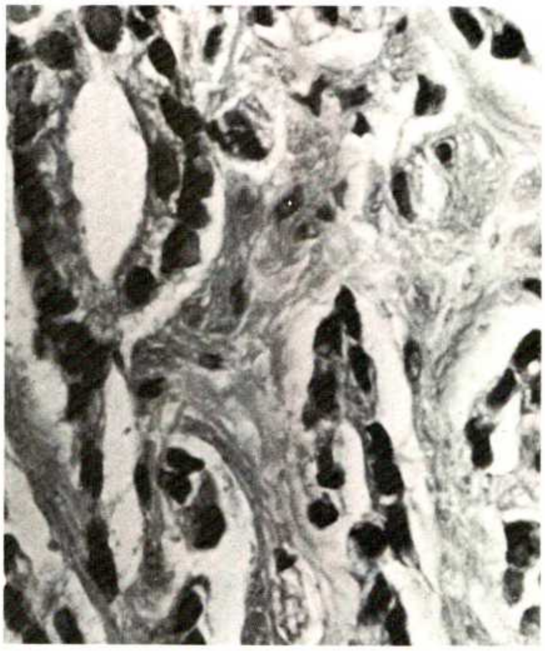

Fig. 2

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British Journal of Urology (1979), **51**, 50

Rupture of a Hydronephrotic Pelvic Kidney

Case Report

A 23-year-old male was admitted with a history of blunt trauma to the abdomen. On the following day he had haematuria with colicky abdominal pain predominantly in the right iliac fossa. High dose excretion urography revealed a left hydronephrotic pelvic kidney overlying the right side of the sacrum, with perirenal extravasion of contrast medium (Fig. 1). The macroscopic haematuria disappeared on the second day after admission, but microscopic haematuria persisted for 7 days. The patient was discharged on the tenth day.

Six weeks after the injury excretion urography showed only a faint left nephrogram. Posterior renal isotope scan did not detect any function in the pelvic kidney. Selective renal angiography was normal. Retrograde pyelography showed a hydronephrotic kidney with a normal ureter. An anterior scan was performed which showed function in the ectopic left kidney (Fig. 2).

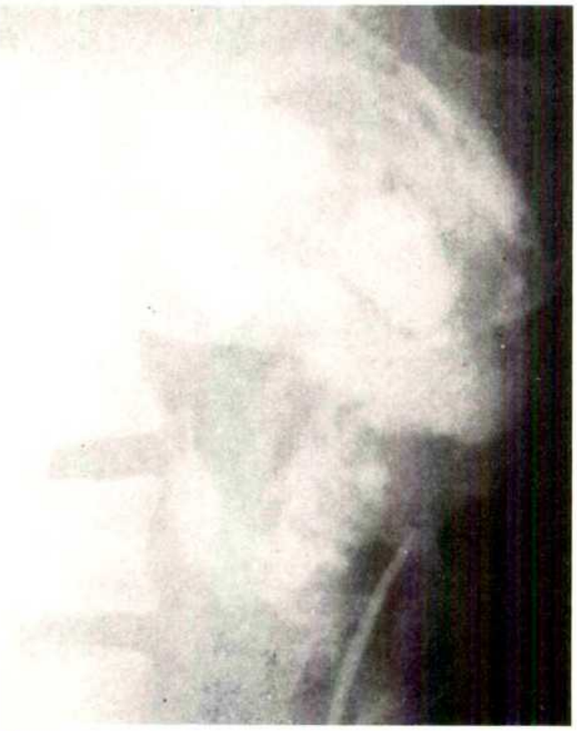

Fig. 1

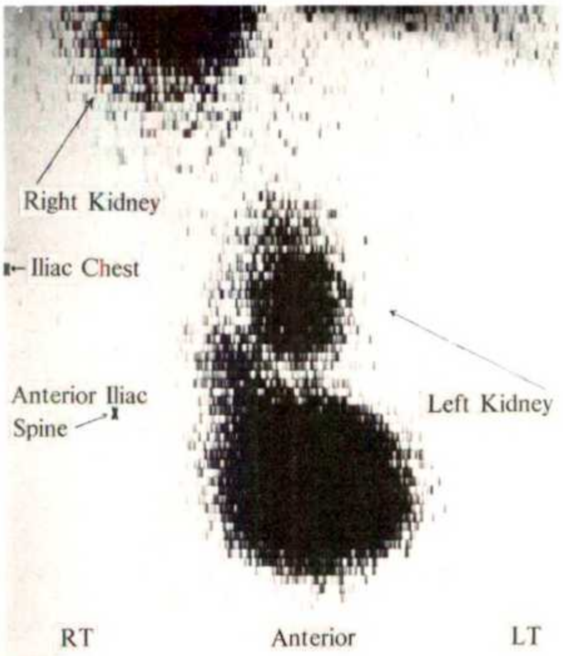

Fig. 2

Comments

Rupture of a pelvic hydronephrotic kidney is rare. Careful search of the English literature revealed only 1 case of ruptured pelvic kidney in a child with renal calculi and infection (Persky and Forsythe, 1962). In our case presacral position of the hydronephrotic pelvic kidney rendered it more susceptible to impact damage.

Reference

Persky, L. and Forsythe, W. E. (1962). Renal Trauma in Childhood. *The Journal of American Medical Association*, **182**, 709-712.

The Authors

A. B. Rao, T. McCartney and T. M. Walker, Departments of Surgery and Radiology, University of the West Indies, Kingston, Jamaica.

British Journal of Urology (1979), **51**, 51

Spontaneous Rupture of the Ureter during High Dose Urography

Case Report

A 30-year-old woman, who had had a stone removed from the upper third of her left ureter 5 years ago and who had developed a stone in her left renal pelvis 3 years ago, was admitted with high fever and a painful swelling in the left lumbar region. Emergency high dose urography without abdominal compression revealed extravasation from the left ureter at the level of the third lumbar vertebra but no stone (Fig.). A few days later she passed a large stone and 4 days thereafter again developed high fever. As urography at this time revealed persistent and increased extravasation, operation was carried out to evacuate the encysted urine and drain the retroperitoneal area. In 7 days the ureter had healed and the patient left hospital in good health.

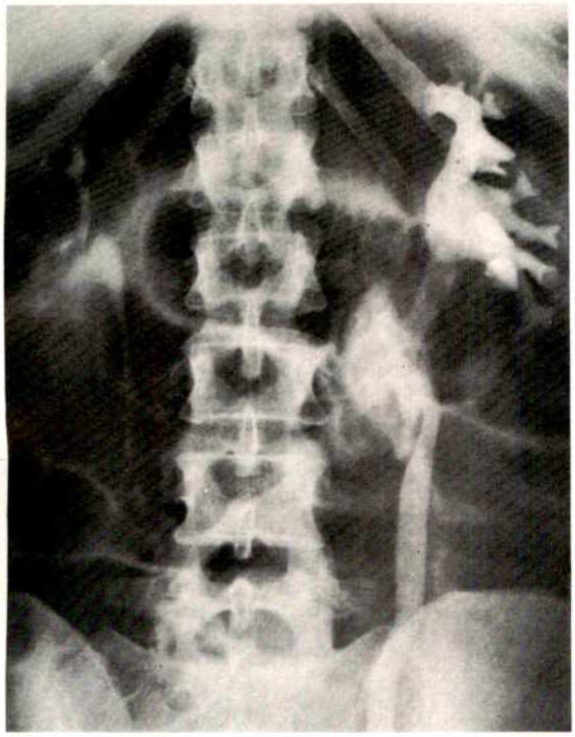

Fig.

Comment

Non-traumatic extravasation of urine is uncommon and usually occurs in chronically diseased or obstructed kidneys. More unusual is spontaneous rupture of the ureter, but with increased use of emergency high dose urography in the investigation of renal colic it has been reported frequently in recent years (Kettlewell *et al.*, 1973; Ramsey *et al.*, 1973).

If the urinary tract is acutely obstructed, the increase in intraluminal pressure, augmented by a sudden diuretic load of urographic contrast medium, may rupture it at the weakest point. In a healthy tract the weakest point is at the caliceal fornices, but extravasation at this level is usually of little importance.

Rupture of the upper third of the ureter, as in our case, is unusual. We think that the ureterotomy 5 years previously had made the upper third of the left ureter thin and inelastic.

References

Kettlewell, M., Walker, M., Dudley, N. and de Souza, B. (1973). Spontaneous extravasation of urine secondary to ureteric obstruction. *British Journal of Urology*, **45**, 8-14.

Ramsey, E. W., Jarzylo, S. V. and Bruce, A. W. (1973). Spontaneous extravasation of urine from the renal pelvis and ureter. *Journal of Urology*, **110**, 507-512.

The Authors

T. Becopoulos, M. Likourinas and G. Pliotas, Department of Urology, King Paul's Hospital, Athens, Greece.

British Journal of Urology (1979), **51**, 52

Conferences and Courses

British Association of Urological Surgeons: Annual Meeting

Bristol. 4-6 July 1979.

Further particulars from the Honorary Secretary, The British Association of Urological Surgeons, at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Institute of Urology (The University of London)

Programme of Seminars for 1979

16-17 March: Urology for FRCS
29 May-1 June: 1-week course in Operative Surgery
2-3 July: Recent advances in the management of Urological Malignancies
12 March-18 May: 10-week course covering the whole range of Urological Practice.

Further details from: The Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2. Telephone: 01-836 5361.

31st Congress of the German Society of Urology

Munich. 17-20 October 1979.

Further information from: Professor W. Mauermayer, Ismaningerstrasse 22, D-8000 München 80, Federal Republic of Germany.

Edinburgh Urological Festival

Edinburgh. 3-5 September 1979.

The first 2 days will be devoted to original papers, preference being given to those submitted by trainees in urology. The third day will be a teach-in by invited speakers.

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG.

International Conference on Urinary Calculi

Perth, Western Australia. 4-8 August 1979.

The Conference will include sessions on: Theories of Stone Formation, The Epidemiology of Stone Diseases, Metabolic Inter-relationships, Medical and Surgical Treatment, Prevention of Stone Formation.

Further information from: Assoc. Professor J. G. Brockis, International Conference on Urinary Calculi, University Department of Surgery, Royal Perth Hospital, Box X2213, G.P.O., Perth, Western Australia 6001.

Australasian Society of Nephrology. Annual Meeting

Perth, Western Australia. 8-11 August 1979.

Further information from: Assoc. Professor J. G. Brockis, University Department of Surgery, Royal Perth Hospital, Box X2213, G.P.O., Perth, Western Australia 6001.

International Symposium on Staghorn Calculus Disease

Ghent, Belgium. 17 March 1979.

This Symposium is organised by the Belgische Vereniging voor Urologie and further information may be obtained from W. De Sy and W. Oosterlinck, Department of Urology, University Hospital, B-9000 Ghent, Belgium.

18th Congress of the International Society of Urology

Paris. 24-29 June 1979.

Further particulars from: Professor Alain Jardin, Congrès Urologie, P.M.V., B.P. 246, 92205 Neuilly Sur Seine, France.

Organisers wishing to have details of their courses and conferences published in the Journal should send details to J.E. Newsam, Western General Hospital, Edinburgh EH4 2XU.

British Journal of Urology (1979), **51**, 53

C.-E. Alken Prize 1979

A prize of 10,000 Swiss Francs is awarded each year to the author who submits the best unpublished work in the field of urology. The closing date for submission of manuscripts is 1 October 1979. Further particulars may be obtained from Professor E. J. Zingg, Department of Urology, Inselspital, CH-3010 Berne, Switzerland.

Book Reviews

Living with Renal Failure. Edited by J. L. Anderton, F. M. Parsons and D. E. Jones. Pp. xi + 281. Lancaster: MTP Press Limited, 1978. Price £8.95.

This book is the Proceedings of a Multidisciplinary Symposium held in 1977. There are 5 sections concerning needs, economics, clinical problems, psychological and personal aspects, and practical management of end-stage renal failure. The contributors have a great experience of the subject which is most evident in the discussions. The book gives a balanced view of the "state of the art" and will appeal to all involved in this multidisciplinary subject.

Metabolic Consequences of Chronic Renal Failure. Michael R. Wills. Second edition. Pp viii + 216 with 15 illustrations. Aylesbury: HM + M Publishers Ltd, 1978. Price £10.50.

The title of this book is quite precise: it does not cover the management of chronic renal failure by dialysis and transplantation. Although the main appeal of this book will be to nephrologists and chemical pathologists, the urologist will find the summaries at the end of each chapter invaluable. The second edition has a full and up to date reference section for those in need of even greater detail.

Clinical Lymphography: Golden's Diagnostic Radiology. Edited by M. E. Clouse. Volume 7. Second edition. Pp xv + 326. Baltimore: Williams and Wilkins Co., 1977. Price $35.00.

This book provides a lucid and comprehensive account of a complex and at times confusing subject.

The format is logical, with excellent chapters covering history, anatomy, physiology and technique as well as interpretation of both benign and malignant disease processes. While much of the information is by no means new, it is presented in a concise and authoritative manner and complemented by many good photographs and an extensive bibliography. Chapters on radionuclide lymphography and the use of immunoglobulins bring the reader up to date with advancing areas and the total package represents a more than adequate standard text for anyone interested in the subject.

Relevance to urological practice is limited to the staging of solid tumours of the genitourinary tract and it is unfortunate that the UICC classification is not used in this book. Rather old figures quoted for prostatic carcinoma metastases are at variance with more recent studies, which suggest higher incidences in all stages.

Emphasis is laid on accurate interpretation of nodal metastases. False negative rates are as expected, while uncharacteristically low false positive rates may reflect the aggressive surgical approach to diagnosis and treatment of abdominopelvic lymph node disease.

The urologist who reads this book will surely appreciate the considerable time, effort and expertise that are required of any diagnostic radiology department providing a lymphography service.

Postgraduate Nephrology. Roger Gabriel. Second edition. Pp. 238. London: Butterworths, 1978. Price £6.75.

As Professor Milne points out in the foreword, the aim of this short monograph is to present modern views of practical nephrological practice as concisely and accurately as possible. The author has succeeded admirably in this task. There has been an explosion in knowledge in the field of nephrology over the past 10 years and a number of large textbooks have appeared on the market. These are bewildering to the postgraduate studying for higher examinations or preparing himself for the practice of nephrology at House Officer or Registrar level. In 200 pages, the whole field of nephrology from routine examinations of the urine, through infection and immunology of the kidney, renal failure, dialysis, transplantation, the kidney in hypertension and pregnancy, and renal tubular disorders are fully described. There is a useful chapter listing the various nephrological syndromes and a series of multiple choice questions and illustrative case histories. At £6.75 this monograph is obligatory reading for anyone wishing to acquaint himself with the fundamentals of nephrology.

Advances in Nephrology. Edited by J. Hamburger, J. Crosnier, J.-D. Grunfeld and M. H. Maxwell. Vol. 7. Pp. 333. Chicago, London: Year Book Medical Publishers Inc., 1977. Price £28.50.

The seventh volume in this series of "Advances in Nephrology" from the Paris Necker Hospital continues the high standard of review in relation to controversial areas of nephrology. However, there is some confusion in the layout of the chapters, as indicated by the Table of Contents. Thus Part 1—The Kidney in Cirrhosis of the Liver—includes 2 chapters on sodium and mineralocorticoids in normal and abnormal pregnancy and echo tomography in urology and nephrology. Part 2—Aldosterone and the Kidney—contains 7 excellent chapters on this topic and a further chapter on glomerulonephritis in severe bacterial infection with and without endocarditis. Part 3—The Kidney in Gammopathies—contains a useful chapter on current views on immunoglobulin abnormalities and a chapter on renal consequences of narcotic abuse, which would not generally be regarded as a gammopathy. Finally, there are 2 useful chapters on haemofiltration and the HLA complex.

Despite their arrangement, the content of the chapters is up to date and serves as a useful addition to the literature in the field of nephrology.

Genitourinary Problems in Women. Jack R. Robertson. Pp. 149. Springfield, Illinois: Charles C. Thomas, 1978. Price $16.75.

Any attempt at drawing attention to dysfunction of the female bladder and urethra is to be welcomed. This is a concise book with excellent diagrams and photographs on the subject. The historical background blends in well with the more recent developments. The section on anatomy and physiology and the evaluation of urinary incontinence is illuminating and valuable.

The major section of the book demonstrates the remarkable versatility that the author has found for his urethroscope using gas as a medium. The cystometric traces and discussion will be valuable to all doctors presently using gas urethroscopy and cystometry. Dr Robertson's appraisal that urologists use the female urethra to rest their male cystoscopes on may have an element of truth in it, but to suggest that the female bladder and urethra should fall into the province of the gynaecologist may strike a discordant note in the hearts of those trying hard to establish a multidisciplinary approach to lower urinary tract dysfunction.

All in all, this book will be a valuable aid to doctors using gas urethroscopy and cystometry in their practices.

Sodium and Water Homeostasis. Contemporary Issues in Nephrology. Edited by B. M. Brenner and J. H. Stein. Vol. 1. Pp. 250. Edinburgh: Churchill Livingstone, 1978. Price £15.

This is the first of a series of monographs which will appear at 6-monthly intervals over a cycle of 7 years. It is the aim of the series to provide a concise and practical review of the pathogenesis, clinical significance and management of a broad array of topics of importance to the nephrologist and urologist.

Volume 1 reviews the issues of sodium and water homeostasis. Four chapters cover water metabolism and hypo-osmolar syndromes, the renal regulation of extracellular fluid volume, sodium depletion states, and disorders of sodium and water metabolism and their effects on the central nervous system. The remaining chapters cover the kidney in congestive cardiac failure, liver disease, nephrotic and nephritic oedema, idiopathic oedema, and the physiological basis and clinical use of diuretics.

Each author has responded to the editors' request that he should present a "thoughtful exposition and synthesis of each topic incorporating new facts, ideas and concepts essential to our present understanding". The chapters are well illustrated and there is a full list of references at the end of each chapter.

This book is recommended to urologists and nephrologists who wish to come to terms with the problems of sodium and water homeostasis and the series as a whole should act as a useful source for extending knowledge in the areas of renal pathophysiology, diagnosis and therapeutics.

Myelomeningocele. Proceedings of Multidisciplinary Symposium, 1976. Edited by R. L. McLaurin, Pp. xi + 850. New York: Grune and Stratton, Inc., 1977. Price $45.00/£31.95.

The Symposium was organised by the Cincinnati Center for Developmental Disorders and held concurrently with the Annual Meeting of the Spina Bifida Association of America, which is a parents' organisation.

The book is divided into 4 parts and succeeds in its aim of providing a comprehensive review of the "present state of the art" of looking after myelodysplastic children. The first part is called "General Considerations" and includes chapters on ecology, pathology, social and family factors. The second part is on neurosurgery, the third on orthopaedics and the fourth on urology. The fourth part runs to some 200 pages and contains 14 papers on such topics as the neurophysiology of micturition, the pathophysiology of incontinence, electrical devices, urinary diversion and sexual problems. It stresses the need to utilise surgery with restraint because neurological phenomena may change and because the long-term results of urinary diversion are poor.

The book is profusely illustrated, well indexed and extensive references are given at the end of each chapter. The whole book can be recommended to anyone concerned with the treatment of patients with spina bifida, and the final part on urology to surgeons concerned with treatment of neurogenic bladder from whatever cause.

Abstracts of the Proceedings of the Urological Society of Australasia 30th Annual General Meeting, Adelaide, Australia, 1978

President: P. A. Harbison (Adelaide)
Honorary Secretary: H. M. Learoyd (Sydney)
Editor: J. P. Maddern (Adelaide)

Renal Autotransplantation and Bench Surgery

By R. A. Straffon
Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.

Renal autotransplantation with or without extracorporeal ("Bench") surgery has been performed for a variety of conditions with increasing frequency. As a result of this experience, the operative technique has been refined and the relative indications and contraindications for the procedure have been developed.

Autotransplantation with or without "Bench" surgery has been performed 11 times in 9 patients at the Cleveland Clinic. Indications included renovascular hypertension, severe ureteric injury, failed supravesical diversion and renal cell carcinoma in a solitary kidney. In addition, donor artery reconstruction on the "Bench" was carried out prior to renal transplantation in 29 cases.

Based on our experience and review of the current medical literature, renal autotransplantation with or without "Bench" surgery is a useful addition to the surgical armamentarium of the urologist.

Transurethral Prostatic Surgery: An American View

By R. A. Straffon
Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.

Transurethral resection of the prostate gland is one of the most common procedures performed by urologists, yet many feel uncomfortable in doing this procedure. It is a difficult procedure to teach to Urology Residents and when inexpertly performed the results can be devastating to the patient.

In comparing the various approaches to prostatectomy (e.g. suprapubic, retropubic, perineal and transurethral resection) no one particular operation has a markedly lower mortality rate associated with the procedure. How well the patient does depends much more on the skill and experience of the surgeon. It is my opinion, however, that in a patient with a prostate gland 80 g or less in size and who needs a prostatectomy, a transurethral resection can be done with less morbidity and less discomfort than any of the open prostatectomies.

There are certain complications associated with any surgical procedure and transurethral resection of the prostate is no exception. Bleeding can be troublesome during the operation and good haemostasis must be secured by fulgurating all of the arterial bleeders at the level of the surgical capsule of the prostate. Fluid absorption may occur particularly when the prostatic capsule is open early in the operative procedure and signs and symptoms of water intoxication must be carefully monitored. Extravasation of fluid or perforation of the capsule or bladder may occur. Post-operative vesical neck contracture, incontinence and urethral strictures are later complications that may develop.

In spite of the many complications that may occur, when expertly performed on a properly selected patient, results of transurethral resection of the prostate should be gratifying to both the patient and the surgeon.

Transurethral Prostatic Surgery: A British View

By J. G. Gow
Mossley Hill Hospital, Liverpool

In transurethral prostatic surgery there are still questions which are constantly being asked and it was thought that a British view might be obtained by attempting to answer some of these questions.

1. Is an irrigating resectoscope an advantage?

It is suggested that an irrigating system is an advantage as it reduces the time of surgery, especially in the small bladder; it reduces the amount of fluid that may be absorbed from the prostatic bed and helps in the teaching of post-graduate students.

2. What irrigating fluids should be used?

Glycine is the solution of choice as it is isotonic, and does little harm if it is absorbed and gives excellent vision.

3. Are aminocaproic acid (Epsikapron), ethamsylate (Dicynene) and Frusemide (Lasix) of any help in reducing blood loss?

Epsikapron may be of value in reducing blood loss during the immediate post-operative period, but Dicynene is probably of little consequence. Lasix has the advantage of stimulating the urinary flow rate and helps to prevent the effects of water absorption.

4. Is post-operative irrigation desirable?

It is debatable whether it is an advantage except in those cases when there has been a greater than average blood loss. In these cases the irrigating fluid, which should be saline, combined with Lasix helps to reduce the incidence of clot retention.

5. Are Urodynamics of any help in investigating "patient wish" prostatism?

Urodynamics are an advantage in the younger age group patients as they help to decide which require bladder neck incision and which a formal resection.

A Technique of Transurethral Prostatic Resection

By H. Thomas
Prince Henry Hospital, Sydney, New South Wales

A method of resection used on 3150 cases is described. Laboratory investigations consist of Hb, blood urea and blood grouping without cross matching. The operative position involves absence of pelvic tilting and is done under epidural anaesthesia using 1.5% Clycine as irrigating fluid.

After prostatic assessment the operation commences by resection of the middle lobe, if present, followed by the cutting of a dorsal groove from the bladder neck to the verumontanum. This defines the lateral lobes and involves retrograde cuts proximal to the veru.

Bladder neck resection on the left side follows, removing from 6–12 o'clock until bladder neck fibres are fully exposed. Resection of lateral lobes is carried out in similar sequence from floor to roof, moving the sheath distally while cutting a large gland to remove more tissue with each cut, at the same time swinging the loop into the adenoma. Finally, apical tissue is removed. When haemostasis is obtained the same pattern of resection is performed on the right side.

Complete control of bleeding must be achieved. An artery directing blood on to the lens face is located by resectoscope sheath compression before diathermy. Venous bleeding may require a reduction in flow rate of irrigating fluid to identify. A large venous sinus will not respond to electrocoagulation and should be controlled by traction on a Foley catheter for 2 hours.

Post-operative drainage is for 3 days with the patient discharged on the fifth post-operative day.

Care of the Patient During Transurethral Resection of the Prostate

By K. Burnside
Melbourne, Victoria

Because one cannot judge the size of the prostate and the difficulty of the resection in advance, it is sometimes impossible to remove the gland completely in 1 hour, especially for a trainee. The emphasis on speed leads to poor control of bleeding, with a risk of sphincter damage and reactionary haemorrhage.

Three time-dependent changes occur during a resection:

1. Progressive blood loss.
2. Water without electrolytes enters the blood, even if an isotonic solution is used.
3. Bacteria, if there are any present, enter the blood. Some prostates are infected even when the urine is sterile, and provide a source of organisms. This bacteraemia may lead to fatal septicaemia or bacterial endocarditis.

Blood loss can be measured using standards containing acid haematin, and replaced as it is lost. Water absorption can be minimised by frequent bladder emptying and by keeping the irrigating fluid less than 30 cm above the bladder. Intravenous Mannitol up to a total of 100 g promotes a diuresis and 3% saline provides electrolytes. Up to a litre may safely be given, with Lasix if necessary. All operations should be performed under antibacterial cover to prevent the risk of bloodstream infection. These measures allow the operation to be done without worrying about time.

The operation should be done carefully with constant control of bleeding. It is better to do a good operation slowly than a bad operation quickly.

Problems of Diathermy in Transurethral Resection

R. P. Yaxley
Mater Misericordiae Public Hospital, Brisbane, Queensland

Radiofrequency alternating currents of 300 to 500 kHz passing through tissues produce heat which is related to current density. A correctly applied dispersive plate (indifferent electrode) helps to eliminate tissue damage. The quality of cutting and/or coagulation depends on the intensity and the wave form of the current. Loss of effect at normal settings of the generator requires a succession of checks on the resectoscope, connections, dispersive plate, generator and the irrigating fluid, which must be non-conductive.

Operators may not generally appreciate that a high frequency current can result in potential electrical pathways due to capacitance induction and radiation, which can result in burns and macroshock or microshock if faults develop or proper procedures are not followed.

The importance of generators and associated equipment attached to the patient, e.g. cardiac monitors and their cables, intracardiac catheters, demand pacemakers, endotracheal tubes, metal drip stands, etc. as alternate circuits is stressed. The need for these, where applicable, to meet the requirements of the S.A.A. (and other committees responsible for standards of electrical safety in medical equipment in Europe and America) is essential to minimise dangers to patients and operators.

Problems Associated with Transurethral Resection

By J. Blackman
Sydney Hospital, Sydney, New South Wales

This paper refers to a personal experience of 675 consecutive patients undergoing transurethral resection of the prostate, with special reference to the problems encountered during the procedure.

No operative mortality was encountered in the early post-operative period. Primary haemorrhage occurred in 4 patients, necessitating their return to the theatre. Three of these were controlled by simple endoscopic diathermy and in 1 patient a stitch to the bladder neck suprapubically was required. There were 10 patients with secondary haemorrhage occurring from 1 to 3 weeks post-operatively. All cases were dealt with by catheterisation and evacuation of the clot. Two patients suffered hemiparesis within 24 hours of operation. Three patients suffered pulmonary embolus, one 48 hours after operation and one 3 weeks post-operatively on returning home. All patients were treated with anticoagulants and completely recovered. Septicaemia occurred in 3 patients. All patients were given Ampicillin intravenously unless allergic to penicillin, when intramuscular kanamycin, gentamicin or intravenous tetracyclines was given.

In the later post-operative period a secondary bladder neck stenosis occurred in 12 cases, stress incontinence in 2 cases, epididymo-orchitis in 4 cases and 2 further patients had continuing frequency. Two patients died, one 2 weeksafter operation following a second unrelated operation, and a second 3 weeks post-operatively from congestive cardiac failure.

Problems of blood loss, shock, resection through the capsule and fluid absorption were encountered during the procedure. Blood loss and shock were treated as they occurred. Resection through the capsule occurred quite frequently, usually towards the end of the procedure and no untoward effects were observed. The breaches were usually small and of no consequence; however, in a large breach of the capsule resection must be stopped immediately and continued later. Fluid absorption seems directly proportional to the time of resection and the pressure of the irrigating fluid. Absorption of the irrigating fluid was kept to a minimum by keeping the pressure at approximately 60 cm of water during resection. Glycine or 4% dextrose was used in a few patients in the present series but in the vast majority the irrigating fluid was sterile water.

Finally, close co-operation between the anaesthetist and the urologist is very important in minimising the complications of transurethral resection of the prostate.

A Comparison of Intermittent and Continuous Irrigation in Transurethral Resection

By W. Johnson

Repatriation General Hospital, Melbourne, Victoria

Initial experience with the continuous irrigation system was not up to expectations. Intravesical pressures were then measured during a resection in a patient with a suprapubic tube and subsequently in the in-flow line after this had been shown to bear a consistent relationship to intravesical pressure.

Pressure measurements were also made with the conventional resecting system with intermittent bladder emptying and where the bladder capacity was small and/or the gland large, consistently high pressures were reached which must be associated with fluid absorption.

High intravesical pressures with the continous system were shown to be related to the position of the resectoscope in the fossa, blockage of the return holes of the resectoscope outer sheath and faults with suction. These could usually be corrected, but only if the operator was aware the pressure was high.

In the early operations 75 cm H_2O in-flow pressure was used with out-flow suction of 15 cm Hg. After changing to 90 cm H_2O pressure and 25 cm Hg suction, operating conditions were improved and bleeding was less with better haemostasis.

It should be emphasised that when using these high pressures larger amounts of irrigating fluid are used and if a fault occurs in the system a rapid rise in the bladder pressure occurs (depending on bladder capacity) and for this reason measurement of intravesical pressure is advocated.

Although it has proved time-consuming, there appear to be distinct advantages for the continuous irrigation system.

Irrigating Fluids in Transurethral Resection

By M. Drummond

Royal Prince Alfred Hospital, Camperdown, Sydney, New South Wales

The problems relating to fluid absorption during transurethral resection of the prostate have been well documented. Studies have shown haemolysis using water, rapid fluid absorption with high hydrostatic pressure of irrigating fluid and hyponatraemia resulting from water absorption.

Unavoidable pre-disposing factors are pre-existing cardiac and/or renal disease and advanced age. However, a number of pre-disposing factors are under the control of the resector: length of time of resection, hydrostatic pressure, and type of irrigating fluid.

An initial study of 20 patients was carried out to assess the degree of haemolysis and biochemical disturbance. Glycine (1.5%) was used as irrigating fluid and hydrostatic pressure was limited to 45 cm water.

In the follow-up study of 10 patients, the aim was to determine the volume of fluid absorbed during the course of a routine transurethral resection and the glycine was labelled with radio-iodine, and again the hydrostatic pressure was limited to 45 cm water.

The initial study showed no biochemical disturbance or evidence of haemolysis. The follow-up study showed significant fluid absorption ranging from 0–926 ml.

In summary, significant fluid absorption was demonstrated during the course of a routine series of transurethral resections. However, using glycine irrigation and with controlled hydrostatic pressure, no haemolysis or biochemical disturbance has been demonstrated.

One Thousand Transurethral Resections—Results and Complications

By J. P. O'Collins

Prince Henry's Hospital, and Frankston Community Hospital, Melbourne, Victoria

One thousand resections for bladder neck obstruction were taken randomly from 3000 and studied. The average follow-up was 6.2 years and the average age 70.2 years. Retention was the presenting symptom in 34% while 20.3% had atonic bladders. At operation 37% had urethral resistance to 28FG sound. In these a urethrotomy or meatotomy was done. The average weight of the gland was 32.2 g when weighed in the theatre and 21.6 g when weighed after fixation with formalin.

Histological examination showed that 86.7% were benign, of which 2.6% later presented as carcinoma; 21.6% showed inflammatory changes and the remaining 13.3% were carcinomatous.

Hospitalisation of 90.4% was under 8 days after operation. Delayed discharge was related to an associated orchiectomy, cystostomy for atonic bladder or stricture, vesical calculi, haemorrhage, further operation, septicaemia and renal failure. The range of stay in hospital was 9 to 25 days with an average of 12.8 days.

Pre-operative mortality was 0.5%. This followed myocardial or cerebrovascular complications.

Results of Open Prostatectomy

By M. Hamilton

Royal Adelaide Hospital, Adelaide, South Australia

A personal series of 233 open prostatectomies is presented. Operation was performed in 143 cases for obstructive symptoms and in 90 for retention. Average age was 65 years, 4 patients being over 90. There were equal numbers of retropubic and transvesical operations. Bladder neck reconstruction was also done in 12, and diverticulectomies, plication of bladder, or partial cystectomy in 27 cases. Two hundred and eighteen were benign: average weight was 30 g. Complications were heavy primary or secondary haemorrhage in 10 cases, usually treated by endoscopy. Wound infections in 7 cases caused 1 day above average hospitalisation and caused 1 wound hernia later. Meatal strictures occurred 4 times and a significant urethral stricture once. Sounds were passed 24 times in 14 patients for various reasons. Orchitis occurred 3 times post-operatively and 3 patients required a transurethral resection at a later date. The only incontinence was partial in a partial paraplegic. One patient developed vascular problems in a leg immediately post-operatively and required bypass surgery. The only death was from either heart failure or embolus at home 9 days after discharge.

The average hospital stay was 11.9 days post-operatively, the shortest being 5 days and the longest being 27. The average follow-up was 8 months, the minimum being one month and the maximum 12 months.

Cryosurgery of the Prostate Gland

By N. A. Green

Norfolk and Norwich Hospital, Norwich

The management of prostatism in high risk patients presents a challenge to urologists, anaesthetists and physicians. The majority can be treated by conventional open or endoscopic prostatectomy. A hard core of patients remains basically unfit for major procedures where the metabolic effects of trauma may prove unacceptable; "cryosurgical" prostatectomy is a good alternative. Using a simple blind technique and limiting the duration of freezing according to the size of the prostate gland, the Frigitronics apparatus with liquid nitrogen as a refrigerant has proved a reliable and versatile instrument.

Leaving a silastic catheter indwelling for 4 weeks, or longer if necessary, allows tissue degradation and *in situ* dissolution or separation to take place. The amount of tissue "removed" may not be as complete as with conventional prostatectomy, but the functional results are good, particularly in those patients with medium and large benign glands.

The high risk group includes those patients with severe respiratory and cardiac problems, coagulation defects and advanced malignancy in other sites. Others with marked prostatism and colonic cancer have undergone the appropriate colectomy and a cryosurgical procedure under the same anaesthetic.

Providing care is taken, extraprostatic complications need not be a problem and serious infective complications and symptomatic urinary infection have been much reduced with prophylactic Septrin therapy.

Early discharge from hospital is possible in the majority of patients who accept the limited period of catheter drainage prior to its removal in hospital.

The technique has a place in those patients who will tolerate a short-lived operation and can be confidently recommended as a useful procedure providing a simple technique is adopted.

The Pathophysiology of Acute Retention of Urine

By E. P. Arnold, J. N. Baxter and W. L. Wright
Department of Urology, University of Otago Medical School, Dunedin, New Zealand

Retention may result from either impaired detrusor contraction or an increased urethral resistance, or perhaps both. Twenty-six consecutive patients admitted in acute retention were compared with an age-matched group of 26 admitted electively for prostatectomy, to illustrate some factors in the pathophysiology. None of the patients had detectable neurological disease.

A. *Bladder Factors*

Detrusor overstretch may have precipitated retention in 5 of the 26 cases: 4 due to alcohol diuresis and 1 to diuretic drugs.

Prolonged overstretch, as in the lower motor neurone neuropathic bladder, may result in considerable impairment of voiding efficiency, and has been shown to be followed by intercellular deposition of collagen disruption of nexus junctions.

Acute overstretch, however, as in acute retention or in Helmstein distension, is rarely followed by voiding difficulties. Furthermore, detrusor pressures measured in acute retention are usually high and are capable of rising even higher by attempts at voluntarily voiding, or with carbachol stimulation.

Other causes of acute retention include smooth muscle relaxant drugs, and an impaired micturition reflex due, for example, to the peripheral neuropathy of diabetes or disc protrusion.

B. *Outlet Resistance Factors*

Sudden swelling of the prostate caused by infection, haemorrhage or infarction may precipitate retention. Infarcts were present in 6 of 26 acute retentions compared to 1 of 26 elective operations.

Lymphocytic infiltration of the gland was significantly less prominent in glands removed from the elective prostatectomy group compared to the retention group.

Urethral pressure profile studies suggest there could be paradoxical tightening of the bladder neck during detrusor contraction. This could be secondary to global hypertrophy of the detrusor in the face of obstruction, or because the mechanics of the bladder neck, altered by the enlarged prostate, reduce its efficiency of opening.

"Stress" and its resulting alpha adrenergic stimulation may increase the urethral resistance. Five of 26 patients had a history of significant stress due to anxiety, recent major surgery, or a heart attack. Some authors have reported success in recommencing voiding when an alpha blocker is given. Prior to catheterisation 10 additional patients in acute retention were given intravenous Phentolamine, but only 2 were able to void following it. To be successful it would need to be given early before detrusor overstretch occurred.

Detrusor-sphincter dyssynergia, indicating failure of sphincter relaxation during detrusor contraction, is a feature of some patients with an upper motor neurone lesion, but sphincter EMG studies in patients with prostatic obstruction have been normal in showing no activity during voiding.

In summary, the pathogenesis of acute retention in non-neurological patients is not entirely clear. An increase in urethral resistance may be of more importance than the concept of the fatigued or overstretched detrusor. The significance of the decompensated detrusor needs further investigation.

Urodynamic Assessment of Prostatic Obstruction

By M. Rao, R. Ryall and V. Marshall
Flinders Medical Centre, Adelaide, South Australia

The use of drugs and other procedures to overcome outflow obstruction in males need to show substantial advantages before they are likely to supplant the effective and relatively safe techniques of transurethral resection or open prostatectomy. In an attempt to provide more information about what happens to the bladder neck and proximal urethra during prostatectomy, 57 patients were subjected to cystometry, urethral pressure profile and urinary flow rate measurements. Prior to operation approximately two-thirds of the patients were found to have small capacity (<250 ml), unstable bladders.

In the 24 patients studied post-operatively, those considered previously to have a small capacity, unstable bladder were now found to have a normal capacity, stable bladder. It appeared therefore that the unstable bladders observed before operation were secondary to obstruction and this instability was unlikely to affect the final result. The length of the urethral pressure profile was found to correlate with the size of the gland, and prostatectomy resulted in a shortening of the profile with a loss of the prostatic plateau. However, the percentage reduction of the original profile length was not found to correlate with subsequent flow rates. Thus, while abolition of the prostatic peak and shortening of the urethral pressure profile were common observations, they do not alone appear to provide sufficient information to define a satisfactory operation as judged by the improvement in flow rates.

Retention of Urine and Disc Disease

By D. Golovsky
Repatriation General Hospital, Concord, New South Wales

Eleven cases of retention of urine are presented associated with central prolapsed intervertebral disc. The majority of patients presented with acute retention without antecedent urinary tract problems. Two patients presented with chronic urinary tract infective symptoms and on examination had large residual urine. Eight patients had a neurological deficit that could be attributed to the prolapsed disc. Seven of the 11 discs were at the level of L 4/5, at L 1/2, 2 at L 3/3 and 2 lumbosacral. Laminectomy and removal of the disc compression resulted in alleviation of retention in 7 to 17 days. One patient who had suffered disc compression for a prolonged period with marked saddle anaesthesia had residual bladder symptoms of incontinence. Four patients had continued back pain following surgery.

It is believed that a central disc prolapse must be excluded in any case of unexplained retention of urine, especially in females. Care should be taken when making the diagnosis of psychogenic retention and the services of a neurologist would appear to be essential in all cases.

The Effects of Distal Obstruction on the Prostate

By R. M. Chambers
Auckland Hospital, Auckland, New Zealand

Distal obstruction (post-gonococcal urethral stricture) was associated with severe bladder outlet obstruction in 50% of 761 cases seen in Uganda during 1968–70. Clinically the prostate was shrunken, fibrotic and contained one or more cavities which filled with urine during cystography. The bladder neck was felt as a rigid shelf with the straight urethral dilator and failed to open during voiding.

Benign prostatic hypertrophy was seen in less than 15% of cases, and simple bladder neck incision was effective if carried well down into the prostate in the remainder.

Histological examination of autopsy specimens of prostate in stricture cases revealed gross destruction of gland tissue, acute-on-chronic inflammation, cavitation and fibrosis in glands from young men. It is suggested that reflux of urine under high pressure during voiding creates a chemical inflammatory process, and that bacterial infection occurs only after complications or instrumentation.

The Management of Staghorn Calculus

By R. A. Straffon
Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.

Any intervention within the urinary tract places the kidney in jeopardy. Staghorn calculi are particularly challenging problems because they are often difficult to remove, are usually associated with infection and/or obstruction and they tend to recur unless the urinary tract infection can be cleared. In addition, staghorn calculi may lead to renal failure.

All patients with staghorn calculi should have a thorough evaluation to determine the aetiology of the stone disease. Although in nearly all cases the stones are associated with a urea-splitting bacilluria, occasionally patients with cystinuria or hyperparathyroidism will be discovered.

After a complete urological evaluation the staghorn calculus should be removed and, if present bilaterally, the operation should be staged at about 4- to 6-week intervals. Appropriate antibiotic therapy is started 48 hours prior to the operation and continued after removal of the calculus. If an obstruction in the urinary tract is present, in addition to the calculus, the obstruction should be corrected.

The surgeon removing a staghorn calculus must be thoroughly familiar with the anatomy of the renal vasculature and the collecting system. The Boyce anatrophic nephrolithotomy is usually the operation of choice, but in selected patients a Gil-Vernet approach may be used. In both instances the renal artery is clamped and the kidney is cooled. If additional nephrotomies are required, they must be carefully positioned to avoid damage to the renal artery supplying that particular area of the kidney.

In selected cases the kidney may be so severely damaged that nephrectomy is the operative procedure of choice. Lower pole segmental resection is used only when the parenchyma of the lower pole is virtually destroyed.

If complete removal of the staghorn calculus is achieved and the urinary tract infection can be cleared, there is a good chance that there will be no recurrence of the calculus.

Surgery for Staghorn Calculus — Auckland Series 1972/1976

By W. Macky
Auckland Hospital, Auckland, New Zealand

During a 5-year period from 1972 to 1976, 61 patients had operations for staghorn calculi. Five had bilateral calculi. A total of 66 operations was carried out. Where feasible, the calculi were removed by extended pyelolithotomy and radial nephrotomy with local renal hypothermia to 20°C.

The average age was 40 years, the oldest patient being 77 and the youngest 9 years.

There was a marked female predominance, 87% of the patients being females. The disease was much more common in Maoris. In 1971 Maoris numbered 7% of the population but 31% of the patients in this series were Maoris. Maori women are prone to obesity, gout and arteriosclerosis and they tend to have large families. Further work is needed to determine whether there is a relationship between hyperuricosuria and the mixed phosphatic or "cast" calculi which were commonly found in this group.

Fifty-nine per cent of the patients had *Proteus* urinary infection. Eighteen per cent had other mixed infections and 23% had sterile urine.

The 66 operations included 19 nephrectomies. Conservative surgery was attempted in 47 cases and of these, 2 resulted in nephrectomy due to uncontrollable bleeding in one case and incomplete removal of calculi after 3 hours of hypothermia in the other.

There was no operative mortality.

The calculi were completely removed in 80% of the cases and post-operative renacidin irrigation was used with appropriate safeguards when fragments remained.

Post-operatively there was a high incidence of ureteropelvic junction obstruction due to stricture. Thirty-five of 44 patients who had conservative operations had post-operative IVPs and of these 8 (23%) were found to be obstructed. The cause of these strictures is uncertain but they may have been due to unavoidable damage to the oedematous, chronically inflamed, friable renal pelvis during dissection, or interference with the blood supply may have been caused by deep dissection in the hilum and the flap type of incision advocated by Gil Vernet. An unduly large ureterostomy or pyelostomy tube may have caused pressure necrosis of the urothelium.

Of the 8 cases of post-operative ureteropelvic junction obstruction, 4 had so-called Parrot-Beak calculi extending into the upper ureter, presumably causing mucosal damage at the ureteropelvic junction.

Despite controlled hypothermia, significant ischaemic damage occurred in 1 of 3 solitary kidneys following prolonged surgery. Acute tubular necrosis may be minimised by the intravenous injection of Mannitol 10 min before the renal artery is clamped. The effect of intra-arterial injection of Inosine after clamping is under investigation.

Complete removal of the calculi was achieved in 80% of the cases. The true recurrence rate after complete removal of calculi was 14% and the overall recurrence rate was 33%.

The 5-Year Fate of 57 Attempted Conservative Staghorn Calculus Operations

By R. B. Brown
Alfred Hospital, Melbourne, Victoria

The results of attempted staghorn calculus surgery were assessed in terms of intravenous pyelography, symptoms, post-operative urinary tract infection and residual calcification. In general the results were satisfactory, particularly the improvement in renal function and relief of symptoms. There were no operative deaths but 2 nephrectomies were performed because of technical difficulties and there were 2 further uraemic deaths within 5 years.

Of the 57 operated kidneys 40 were initially radiologically cleared of all calcified material. Thirty-two of these kidneys remained calcium-free over the 5-year period, despite a 6% incidence of post-operative infection, but 8 recalcified and of these 8, 7 were infected. Only 1 newly recalcified area has so far achieved a size greater than 1 cm^2.

Of the 17 kidneys with residual calcified material after the operation, 41% were infected and there was a 53% overall increase in size of calcification, although a significant increase in area was usually related to the size of the original post-operative calcified area and in only 3 cases has exceeded 1 cm^2, and produced symptoms sufficient to justify further surgery.

The failure to remove calcified material greater than 1 cm^2 in size and persistent post-operative renal infection were the 2 main factors in this series responsible for significant post-operative depressed renal function, new or additional calcification and persistent or recurrent symptoms.

Saline Ice Slush Hypothermic Anatrophic Nephrolithotomy for Complex Coralliform Calculi

By R. Parisi
Townsville Base Hospital, Townsville, Queensland

Whilst many coralliform calculi can be removed via an intrasinus approach, from 1973 to 1977 10 complex coralliforms were removed from 7 females by a Saline Ice Slush Hypothermic Intersegmental Nephrotomy (Boyce). A separate apical nephrotomy was required in 6 patients. Decompression by nephrostomy was used in 5 and a ureteric splint in 2. Perirenal Redivac drains were used in all 10. Operation time was from 2.5 to 4 hours with an ischaemic time of from 1 to 2.5 hours (average 1.8). Hospitalisation was required from 8 to 20 days (average 11). Transfusion was required in 2 cases.

Ages ranged from 21 to 57 years. Stones were bilateral in 5 patients. Primary hyperparathyroidism with nephrocalcinosis occurred in one case while secondary hyperparathyroidism was found in another. Primary obstructive megaureter was present in one case while 3 were hypertensive. *Proteus* urinary infection was identified in 7 cases and a concomitant *Staph. aureus* infection occurred in one. Ampicillin alone or combined with penicillin G or gentamicin was administered until the drainage tubes were removed and culture sterile, followed by co-trimoxazole prophylaxis for 3 months.

Four of 6 cases followed up to 4 years had sterile urine. Renal function remained stable in all cases. Wound infection occurred in one and a diathermy burn in another case. There was no mortality, haemorrhage or urine leakage. Calculi were totally cleared in 9 cases. One residual fragment, 2 mm in size, was unchanged after 18 months. There were no recurrences but one new contralateral stone occurred.

The procedure appears to be safe and remarkably complication-free. It relieves pain and can prevent deterioration of renal function, pyonephrosis and septicaemia. Total calculus clearance is possible and the recurrence rate low. The advisability, feasibility and availability of safe removal of coralliform stones are stressed.

Calculus Survey

By A. S. Wood
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The study involved 201 unselected urinary calculus patients seen in (private urological) practice over 4–5 years. There were 63 females.

Screening measurements included: serum calcium, phosphate, uric acid, 24-hour urinary calcium, oxalate, uric acid and volume, where possible stone analysis, and where urinary pH or other factors indicated, the short ammonium chloride urine acidification test.

Patients were questioned about diet, analgesics, calcium containing antacids, and at times interviewed by dietitians, both to assess normal diet and to help patients modify their eating pattern.

Follow-up at yearly intervals was done on a postal or consultation basis, depending on patient need. Follow-up was from 1–5 years.

Stasis (including renal tubular ectasia) occurred in 14% (27/201) but only 22% (6/27) did not have some metabolic abnormality or other suggestive stone cause as well.

Fourteen per cent (29/201) probably had a high calcium intake from milk products, calcium-containing antacids or calcium tablets in pregnancy.

Thirty-one per cent (62/201) of patients showed hypercalciuria and of these 28% (17/62) were female.

Thirty-one per cent (62/201) showed hyperuricosuria and of these 18% (11/62) were female.

Thirteen per cent (26/201) showed both hypercalciuria and hyperuricosuria, although not necessarily simultaneously.

Low urine volume less than 1000 ml/day occurred in 17% (33/201) and less than 1300 ml/day in 28% (57/201).

It is concluded that 24-hour urine examinations are far more profitable than serum tests in assessing stone forming factors capable of being treated; these studies also help to monitor advice to produce a daily 2-litre urine output, a task many patients find difficult to follow.

Recent Advances in Stone Formation

By J. G. Brockis
University Department of Surgery, Royal Perth Hospital, Perth, Western Australia

A health survey in Busselton, a coastal town 140 miles south of Perth, has revealed that 1 in 10 males had kidney stones by the age of 60. Analysis of 228 stones collected from patients at Royal Perth Hospital has established a pattern in which 16% are predominantly urate and only 10% contain triple phosphate; the remaining stones are almost entirely calcium oxalate — phosphate calculi.

Studies of the ionic products of calcium and oxalate in urine show that whilst hypercalciuria is not uncommon, small changes in oxalate concentration have a much more profound effect on the product. Urine crystalline growth inhibitors have been measured by a modification of the Robertson Coulter Counter technique and compared against a standard of pyrophosphate.

The stabilisers of urate solutions are electrolytes and organic material plays only a very small part. A fall of pH below 5.4 causes rapid precipitation of uric acid, whilst high levels of urate and ammonium ion result in deposition of ammonium acid urate. Sodium urate is not usually precipitated because of its relative stability in colloidal form.

The Immediate Intravenous Pyelogram in Ureteric Calculi

By W. Johnson
The Royal Melbourne Hospital, Melbourne, Victoria

This study of 123 consecutive patients presenting to the Emergency Department with a provisional diagnosis of renal or ureteric colic was made to evaluate critically the role of the immediate IVP.

During the first 2 months of a 3-month period, all patients with renal or ureteric colic had an immediate IVP and during the third month the attending doctor alone decided if an IVP was needed. All clinical details were recorded at the time of presentation and the subsequent course followed.

A positive diagnosis of calculus could be made in 77 patients and 25 patients had an alternative diagnosis established. In a further 21 patients there were insufficient grounds to make a definite diagnosis but no patient appeared to suffer from this.

The study showed that one-third of patients presenting to the Emergency Department with suspected renal or ureteric colic had an identifiable calculus on a plain X-ray and this offered sufficient diagnostic certainty for decisions regarding immediate management. Where the plain X-ray was negative or doubtful, the immediate IVP offered a high degree of diagnostic accuracy but its use can safely be limited to those patients where exclusion of calculus as a diagnosis is crucial to the immediate management. Where the accuracy of diagnosis is not imperative at presentation, an elective IVP will provide the necessary information for subsequent management and avoid overloading the busy Emergency Department.

Conservative Management of Ureteric Calculi

By M. Hamilton
Royal Adelaide Hospital, Adelaide, South Australia

A retrospective study of cases with a ureteric stone collected over a 13-year period was presented. Cases were rejected if X-rays were not available for re-examination and measurement of the stone size unless the stone size was already recorded. Two hundred and eighteen cases were examined.

In the presenting IVP 29 non-functioning kidneys were noted. In the follow-up IVP on 19, 3 still had poor function and the remainder were normal. Of 54 kidneys showing caliceal dilatation 26 cases had a later IVP which was normal and one showed moderate dilatation. It seemed that unless obstruction was long-standing it was of minimal importance in determining the need for intervention.

One hundred and fifty-four cases were treated conservatively initially and 119 passed the stones without intervention. In those cases where a Dormia stone basket was used a 60% success rate was achieved but in those in whom extraction failed the time intervals before subsequent passage of the stone were the the same as in the untreated group, so failed manipulation did not expedite passage.

Lower ureteric stones less than 4 mm in size passed in 65 out of 75 cases. The other 10 were manipulated and removed or passed. Below 6 mm in diameter only 2 of 101 required open operation. Stones above 6 mm progressively required more intervention.

In upper ureteric stones the critical size of the stone indicating open intervention was 6 mm. Fourteen stones between 5 and 6 mm passed or were extracted when they reached the lower ureter, while 10 were removed by operation.

Apart from the pain initiating investigation there was little morbidity from this conservative approach.

A Method for Measuring Crystal Size

By R. Ryall and V. Marshall
Flinders Medical Centre, Adelaide, South Australia

Many conclusions regarding urinary stone disease have been drawn from the investigations of Robertson and co-workers based on the use of the Coulter Counter to estimate calcium oxalate crystal number and volume. We have re-examined the technique with regard to its value in the assessment of urinary calcium oxalate crystal size and inhibitor activity. The method previously used involved measuring crystal number at constant threshold settings. However, the size intervals over which counts were taken varied from 1 micron (3.8–4.8) to 10 microns (38.6–48.6), with gradually increasing intervals between these extremes. We have modified the technique so that counts are taken over constant size intervals, thus ensuring that the correct emphasis is placed on all particles with respect to their relative contribution to the area under the volume distribution curve.

The validity of using constant diameter intervals, and the resulting improvement in accuracy and resolution, are demonstrated by using a mixture of latex particles of known sizes (2.03, 9.12 and 13.8 microns in diameter). Our technique shows 3 distinct peaks whether results are plotted as number or volume, whereas the original method, though showing a discrete peak at around 2 microns, is unable to distinguish between the other 2.

Finally, we have demonstrated that the incubation solution used by Meyer and Smith demonstrates a significantly greater level of crystal growth and improved reproducibility when compared with that used by Robertson and Peacock.

The Diagnosis and Treatment of Renal Hypertension

By R. A. Straffon
Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.

The National Health Survey done in the United States in 1972 suggested there were probably 30 million patients with hypertension in this country. If we assume that 5% of these may have a surgically correctable cause for their hypertension we can project a rather large group of patients who may be helped by operative intervention.

It is impossible and impractical to study each hypertensive patient, so those patients having clinical features that suggest renal hypertension form the group which must be studied. Our indications for renal angiography are an abnormal intravenous pyelogram with findings suggesting renovascular hypertension and those patients who have hypertension and are under 35 years of age, have an abrupt onset of hypertension at any age, have a sudden exacerbation of pre-existing hypertension, have malignant hypertension, and hypertensive patients with diffuse changes of arteriosclerosis or the presence of abdominal bruit. If the lesion is discovered on renal angiography the renal vein renin should be obtained to see if the renin level is elevated on the diseased side as compared with the contralateral kidney.

A knowledge of the classification of renovascular disease and the natural history of each specific lesion will aid the surgeon in determining which patients should have surgical correction of their renovascular lesion. The angiographic appearance of the lesion has been correlated with the pathological process present to aid the clinician in determining with reasonable accuracy what renovascular disease is present in the patient prior to the operative procedure.

An anterior, subcostal incision is used to approach the renal artery, the incision being placed on the side which is to be repaired, or a Chevron incision can be used to expose both sides simultaneously. In selected patients segmental or total nephrectomy is the procedure of choice. In the majority of patients, revascularisation techniques can be used and the aortorenal bypass graft using autogenous artery or vein is the operative procedure most commonly done in our Clinic. The results of revascularisation should yield a cured or improved rate of nearly 80% when all of the diseased processes involving the renal artery are reported as a group. Better results are obtained generally in patients with one of the fibrous dysplasias of the renal artery than in the patients with arteriosclerosis.

Primary Renin Secreting Tumour of the Kidney

By J. S. Jose

Royal Adelaide Hospital, Adelaide, South Australia

Primary renin secreting tumour of the kidney (juxtaglomerular cell tumour) is a rare but important remediable cause of hypertension occurring in children and young adults. Two of the 11 cases in the literature have been reported from Adelaide by Bonnin, *et al.* Excessive renin secretion from whatever cause produces the clinical syndrome of hypertension, hypokalaemia and excessive aldosterone production. When these symptoms are encountered in a young person (age range 7–37 years, mean age 22 years) a primary renin secreting tumour should be suspected. The diagnosis is confirmed by the finding of marked elevation of the peripheral plasma renin activity in the presence of renal arteriograms displaying a normal renal vascular tree, excluding renal artery stenosis. The renal tumour may not be demonstrated on the renal arteriogram and commonly an intravenous urogram is normal. Selective blood sampling from the renal veins and their peripheral branches can localise the anatomical site of abnormal renin production to permit nephrectomy or partial nephrectomy to be performed for removal of the tumour. Although a few mitotic figures are found on light microscopy of the tumour, none of the reported tumours has proved malignant.

In diagnosis, it is important to differentiate between a primary aldosterone producing tumour of the adrenal cortex and a renin secreting tumour of the kidney. Aldosterone production is elevated in both instances but peripheral plasma renin activity is depressed in primary aldosteronism, and elevated in primary reninism. At nephrectomy, blood pressure falls to normal over the first 6–8 hours post-operatively. There was no sudden fall in blood pressure on removing the kidney in either of the 2 cases studied. Post-operatively, serum potassium and aldosterone levels returned to normal, but in one case a secondary rise in blood pressure and aldosterone levels with depression of serum potassium and peripheral plasma renin activity occurred, probably due to adrenocortical hyperplasia following prolonged renin stimulation. These changes slowly reverted to normal without further therapy. Both of our reported cases remain normotensive at 7 and 4 years respectively.

Caecocystoplasty — A Study of 37 Cases

By J. G. Gow

Mossley Hill Hospital, Liverpool, England

Thirty-seven patients who were treated by caecocystoplasty between 1963 and 1967 were studied. Thirty-one were suffering from tuberculosis, 5 from interstitial cystitis and one had a carcinoma of the fundus of the bladder. The ages ranged from 18 to 70 years. Fourteen had extensive involvement of the kidney, 17 involvement to a lesser degree and 5 had normal kidneys. In 20, nephrectomy was performed and 4 were treated by uterostomy *in situ* prior to the caecocystoplasty, to improve renal function which had deteriorated because of obstruction at the lower end of the ureter.

Six points in the technique were emphasised: (1) extensive mobilisation of the hepatic flexure, (2) incision in the peritoneal covering of the caecal pedicle to prevent tension, (3) the importance of anastomosis of ureters to the terminal ileum before the caecocystoplasty when this was necessary, (4) the importance of leaving as much of the bladder as possible, (5) the importance of making the anastomosis between the bladder and caecum as wide as possible, and (6) the value of covering the anastomosis between the bladder and caecum with omentum.

One of the 6 patients who died developed a squamous carcinoma of the bladder remnant, which may be significant as another patient has shown evidence of squamous metaplasia in the bladder remnant. Renal function improved in 7 out of 10 patients with impaired renal function, which is now not considered a contraindication to this procedure. None of the 10 patients who had a urinary tract infection before surgery subsequently had sterile urine. The infected urine was nearly always symptomless and was ignored as no case of spread to the upper urinary tract occurred.

Urinary Vaginal Fistulae

By H. Awang
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A review of 39 cases of urinary vaginal fistula during the 5-year period 1972–1976 is presented. Thirty-four cases were operated on and of these there were 20 cases of vesicovaginal and 14 cases of ureterovaginal fistula.

Obstetrical complications were responsible for 50% of the vesicovaginal fistulae whereas gynaecological complications caused over 80% of the ureterovaginal fistulae.

The majority (16) of the vesicovaginal fistulae had at least one previous attempt at repair. Repair and excision of the urinary vaginal fistulae were mostly done after a delay of 3 months to allow tissue to heal and inflammation to subside.

Thirteen cases of vesicovaginal fistula had successful repair excision using the modified O'Connor technique using a flap of peritoneum placed between the 2 suture lines. Three cases were successful using the vaginal and combined vaginal abdominal approach. Four cases failed and all were severe injuries involving the bladder neck and urethra.

With the ureterovaginal fistulae the type of operation performed was dependent on the condition of the patient, the degree of impairment of renal function, the extent of injury and the findings at operation.

Life-saving measures such as nephrostomies and drainage of abscess and urinoma were emphasised.

The Baori flap technique was performed in 9 cases, end-to-end anastomosis in 2 cases, reimplantation in 2 cases and nephrectomy in 2 cases. All had satisfactory results.

The Results of Antireflux Surgery in Children

By E. D. Smith
Royal Children's Hospital, Melbourne, Victoria

Antireflux surgery has been performed on 336 ureters in 221 patients (101 Grades I and II, 170 Grade III, 64 Grade IV). Excluding 6 nephrectomies, follow-up excretion urography and micturating cystourethrography have for a minimum of 1 year following surgery been completed on 253 ureters. Four measurements of results are recorded:

1. Persistence of post-operative reflux has occurred in 10 ureters (4%), the incidence differing little in the grade of reflux (2 of 71 Grades I and II (2.8%), 6 of 132 Grade III (4.5%), and 2 of 50 Grade IV (4%)). Of these 10 refluxing ureters only one has required re-operation, the remainder being a trace of reflux only with no infection.
2. Post-operative ureteric obstruction — 9 ureters (3.2%), of which 4 have required re-operation.
3. Post-operative infection has occurred in 42 patients (25%); of these 38 are females of whom 32 had no post-operative reflux or obstruction, i.e. their infection has been shown to be lower urinary tract urethrocystitis. The males had grossly abnormal upper tracts.
4. Comparison of pre-operative and post-operative urography with reference to caliceal dilatation, cortical thickness and renal growth. Of 132 Grade III ureters, 57 were initially normal and 4 deteriorated post-operatively (obstruction), 75 were initially abnormal, 3 deteriorated post-operatively, 37 remained unchanged and 35 improved.
   Of 50 Grade IV ureters, 6 were initially normal and remained normal, 44 were abnormal of which 3 deteriorated, 19 remained unchanged and 22 improved. It is stressed, however, that these are short-term results of 1–8 years only.

In 57 grossly dilated ureters, only 6 were extensively tailored by reduction ureteroplasty above the pelvic brim, of which 2 ureters sloughed. Because of this experience, and with the evidence that linear axial flow in a straight non-tortuous ureter is more important than reduction in lumen diameter, the remaining 51 ureters were straightened out and varying lengths of their lower ends excised, reduction in size being confined to the last 3 or 4 cm of ureter to facilitate the submucosal tunnelling.

In the series 5 ureters sloughed from ischaemia, 2 after tailoring extensively as above and 3 after simple reimplantation. Two were salvaged by transureteroureterostomy and 3 by high reimplantation.

The technique used was that of Leadbetter-Politano with both intravesical and extravesical exposure.

A Screening Technique for the Diagnosis of Intrarenal Reflux

By D. L. Rothwell, P. G. Ransley and A. R. Constable
Institute of Urology and Hospital for Sick Children, Great Ormond Street, London

This is a preliminary report of an attempt to detect intrarenal reflux (IRR) using radionuclides in piglets.

The detection of IRR by radiographic means in children is less than 10% despite evidence that IRR occurs relatively frequently.

Initially it was shown in the piglet that the isotope technetium penetrated the renal cortex during an episode of IRR and remained there.

It was then hypothesised that when technetium reached the renal parenchyma during the period of IRR, there may well be high levels of radioactivity in the general circulation.

In the second experiment blood samples were measured for radioactivity in a number of piglet kidneys that showed IRR.

Finally, the blood levels of radioactivity were recorded using a sensitive gamma probe.

Preliminary results indicate that this technique may have clinical application in children with urinary tract infection and vesicoureteric reflux as a screening procedure.

Helmstein's Hydrostatic Therapy in the Management of Bladder Carcinoma

By F. H. D. Breslin
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Occasionally it is difficult to treat papillomatosis of the bladder by endoscopic means because of the widespread nature of the lesion. When the lesions are so widespread the technique of hydrostatic pressure, first described by Helmstein, may be useful.

In addition, persistent bleeding may occur after irradiation of the bladder and, as an alternative to a salvage cystectomy, Helmstein's treatment with hydrostatic pressure can be used with effect. This applies even when there is residual invasive tumour present.

The technique consists of the introduction of a large rubber balloon into the bladder. The balloon is distended with saline or with glycine to a pressure just exceeding the diastolic blood pressure. This causes tumour necrosis with less severe effects on the intervening mucosa or the blood supply of the deeper layers of the bladder. Pain is completely controlled by epidural anaesthesia for 4 to 6 hours.

The results of a series of 8 patients, including those with papillomatosis and post-irradiation bleeding, show that the technique is effective. Fronded papillary tumours are reduced markedly in size. More solid, raspberry-like tumours do not respond nearly so well but the bladder can be largely cleared of papillary tumours so that resection of the remaining tumours can be carried out.

In the irradiated bladder, particularly in elderly and poor risk patients, this treatment offers a simple method of control of an often distressing problem. It obviates the need for the introduction of substances such as formalin into the bladder.

Helmstein's hydrostatic distension therapy of the bladder is presented as a technique to be used in selected cases. It is relatively non-invasive and easy to perform, and can be repeated on several occasions if necessary.

Experiences with Total Cystectomy

By G. Joyce and D. Lenaghan
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A series of 51 patients treated by total cystectomy during the past 15 years is presented. A protocol which includes pre-operative radiotherapy of 4,000 rads to the bladder and pelvis followed by radical cystectomy has been used in the past 2 years. Failed previous treatment was the indication for cystectomy in nearly half of 51 patients. Results in this group were no different from those in a group having treatment by cystectomy alone.

Operative mortality was 11.8%. At least some of these deaths were preventable. Twenty of the remaining 45 patients died in the first 2 years following surgery. These were mostly high grade, high stage tumours and deaths were mostly due to pelvic recurrence of tumour or metastases. Long-term survival tended to be associated with lower grade and lower stage tumours.

Limited data from the protocol group suggests that increased survival during the first 2 years may be obtained by using pre-operative radiotherapy with total cystectomy. The extent of surgery may be modified in high risk patients but total clearance of tumour will frequently require radical cystectomy with urethrectomy in continuity.

Ureteric Dilatation by Fogarty Catheter

By G. J. Heap
Canberra Hospital, Australian Capital Territory

Access to the lower end of the ureter is notoriously difficult, especially where it passes through the bladder wall. This part of the ureter is occasionally the site of a calculus or transitional cell papilloma. If the pathological process is very near the ureteric orifice, it can be reached by dilating the orifice with a Fogarty catheter (11 mm).

Ureteric dilatation was used in 5 patients. In 2 cases it was possible to treat small tumours by cystodiathermy. In 2 patients with ureteric stones, ureteric dilatation seemed to aid extraction with a Dormia basket. In a third case the basket became entangled in the ureter and open surgery was needed.

The results indicate in most cases an increase in heat of the testis of the side of the varicocele compared to the contralateral side as measured pre-operatively, and show an equalisation of testicular temperatures subsequent to surgery. In a small number of cases other variations are observed and reported.

It is considered that the procedure is a simple non-invasive method of assessing temperature of the testes in varicocele patients, and the thermal changes produced by surgery.

Late Urological Complications of Transplantation

By J. Rogers
Royal Prince Alfred Hospital, Sydney, New South Wales

Three hundred and thirty renal transplants performed at the Royal Prince Alfred Hospital from 1967–1977 were reviewed to look at the late urological complications (from 3 months on). There were 17 urinary tract obstructions, 12 cases of persistent or recurrent bacterial infections, 2 cases of abacterial cystitis and 2 cases of malignancy.

Upper urinary tract obstructions included 1 case of pelviureteric junction obstruction, 6 cases of ureteric obstruction by lymph cysts, 3 periureteric fibroses (2 due to fibrosis, 1 due to an abscess), and 1 ureteric calculus, secondary to dystrophic calcification in the ureter.

Of the 6 lower urinary tract obstructions 4 were due to strictures, 1 to benign prostatic hypertrophy, and 1 to transitional cell carcinoma.

Of the recurrent bacterial infections 2 were due to reflux up the orthotopic ureter, 1 to reflux up the transplant ureter, 3 were secondary to strictures, and the remainder had a varied aetiology. There was 1 case of tubercular cystitis, and 1 of proliferative cystitis. This appeared to improve following a course of Flagyl therapy given for coexistent Giardia lamblia infection of the bowel.

Of 37 malignant tumours in these 330 patients, 2 were urinary. One was fatal (a squamous cell carcinoma of the renal pelvis in a patient with analgesic nephropathy), and 1 was a transitional cell carcinoma of the whole urethra, which was treated by resection and eventual two-stage urethroplasty for stricture, and has apparently been cured.

Operations for obstruction were generally successful, with mean creatinines during the stable phase being 2.6 mg%, rising to 4.0 mg% at diagnosis, and settling back to close to the previous stable level within one month of surgery.

Urinary complications, especially obstructions, must be excluded in a patient with deteriorating renal functions, in whom rejection does not appear to be the obvious cause.

Reversible Renal Failure Due to Renal Artery Occlusion

By B. G. Storey and A. G. R. Sheil
Medical Research Department and Department of Urology, Sydney Hospital, Sydney, New South Wales

When unilateral renal artery stenosis causes hypertension the opposite kidney is exposed to the effects of hypertension, while the ipsilateral kidney, to a varying extent, is protected by the renal artery stenosis. Should stenosis progress to occlusion, renal atrophy or infarction is usual.

However, it is known that collateral arterial supply can maintain viability of kidneys with occluded arteries, allowing recovery of function spontaneously, or following embolectomy. It is also known that reconstructive vascular operations can result in recovery of renal function.

It follows that some patients with renal failure and hypertension might be found in whom advanced nephrosclerosis is confined to one kidney, poor function of the other kidney being due to thrombosis of a stenosed renal artery. The kidney with the occlusion may remain viable because of collateral circulation and may have life-sustaining function following arterial reconstruction.

In 1973 we reported 2 cases of renal artery thrombosis, one with uraemia, and the other with acutely deteriorating renal function. At operation biopsy revealed viability of the kidneys with thrombosed renal arteries.

Revascularisation of the kidney resulted in restoration of function with reversal of renal failure.

We therefore suggested (in 1973) that angiography should be performed more frequently in patients with failing renal function in an effort to discover more remediable vascular lesions, especially in those cases with hypertension and relatively sudden deterioration in renal function. We believed that patients with severe renal artery stenosis and impairment of renal function, who were otherwise acceptable candidates for operation, should be operated on to prevent further ischaemic renal damage and avoid the risk of total renal artery occlusion.

During the past 5 years we have operated upon another 4 patients with severe renal artery stenosis, associated with progressive renal impairment and marked analgesic nephropathy, in the hope of preserving their renal function. Three bilateral renal artery bypass grafts and one right nephrectomy associated with a left renal artery graft were performed. One patient died of post-operative myocardial infarction and 2 patients had to commence chronic haemodialysis at 6 months and 3 years respectively. The last patient remains well after 3 years without any further deterioration of renal function.

Following these rather disappointing results we now believe that those patients who are suffering from marked analgesic nephropathy should not be considered suitable for renal artery surgery, for, at the most, the arrest of the deteriorating renal function can only be regarded as a temporary relief in an inevitable downward path.

The Mechanisms of Injury in Rupture of the Posterior Urethra and their Influence on Management.

By L. M. Harewood
The Royal Melbourne Hospital, Melbourne, Victoria

Twenty-one cases of rupture of the posterior urethra were studied. The aetiology was as follows: 14 pedestrians hit by car, 5 work-related pelvic crush injuries, 2 miscellaneous. The pelvic fractures were classified into 3 main types.

Type A (12 cases): Unilateral fractures of the superior and inferior pubic rami.

It is suggested that this fracture is due to a lateral blow causing the fractured inferior pubic ramus to tear through the urogenital diaphragm, shredding the posterior urethra.

Type B (4 cases): Bilateral fractures of the superior and inferior pubic rami.

This is due to an anterior blow causing the symphysis, prostate and urethra to move backwards, the urethra being disrupted by the posterior part of the perineal membrane.

Type C (4 cases): Diastasis of symphysis pubis and disruption of the sacro-iliac joint.

In this fracture the disrupted symphysis moves backwards, tearing through the urogenital diaphragm and tearing the prostatic attachments.

A retrograde urethrogram was obtained in 12 cases. The site of extravasation was as follows: 4 into the perineum alone; 7 in both the perineum and extraperitoneal; 1 extra-peritoneal only. The extravasation communicated with the fracture site in 4 cases. The stricture formation occurred in the bulb in 2 cases; along the length of the membranous urethra in 11 cases; supramembranous in 1 case; unknown in 4 cases.

The management should be directed towards:

1. Early recognition of the partial rupture by retrograde urethrography and panendoscopy.
2. Avoidance of disturbing the fracture site.
3. Transvesical introduction of a urethral catheter to splint the rupture.
4. Reduction of pelvic fractures.

Control of Bleeding after Renal Biopsy with Epsilon-Amino-Caproic Acid

By B. G. Storey, E. Savdie and J. F. Mahoney
Medical Research Department and Department of Urology, Sydney Hospital, Sydney, New South Wales

Urokinase, the urinary fibrinolytic activator, may prevent formation of an adequate clot after trauma to the urinary tract, thereby promoting prolonged or recurrent bleeding. Epsilon-amino-caproic acid (EACA), which inhibits urokinase, has been used successfully in the treatment of bleeding after prostatectomy and of haematuria in patients with haemophilia and sickle-cell disease. More recently, EACA has also been recommended for treatment of prolonged haematuria following renal biopsy. We report our experience with its use in 6 patients in whom severe or persistent bleeding occurred after percutaneous biopsy of the kidney.

During a 3-year period, 6 patients had a bleeding complication after percutaneous renal biopsy and required transfusion and surgical consultation. Three patients had persistent gross haematuria and 3 perirenal bleeding confined to the retroperitoneal space. Because of severe or prolonged bleeding, each was treated with EACA.

Routine clotting tests, including thrombotest, bleeding time (Ivy), and platelets count were normal in all patients prior to biopsy. Four patients were hypertensive but satisfactorily controlled, and 2 had advanced renal failure at the time of biopsy.

One patient required treatment 5 hours after biopsy because of massive perirenal haemorrhage with life-threatening hypotension; the average time interval between biopsy and initiation of EACA treatment in the others was 14.2 days.

The average dose of EACA was 9.6 g/day, and the mean duration of treatment 17.3 days. No patient required further blood transfusion subsequent to treatment with EACA. The only serious side effect encountered was the formation of persistent clots in the bladder and ureter of patient No. 3, which were successfully treated by ureteric catheterisation and irrigation.

The use of Infrared Thermography in an Assessment of Varicoceles

By A. Fortune
Department of Andrology, Fremantle Hospital, Fremantle, Western Australia

The possible relationship of varicoceles in male infertility has been well documented and various possible mechanisms of the production of infertility have been examined. Thermography has been used to assess testicular temperature variation associated with the presence of a varicocele.

In this study, infrared photography has been used as a simple means of measuring radiant heat. Its use is based on the fact that radiant heat can be quantitatively assessed by the measurement of isotherms which by being selectively filtered and exposed on to a polaroid film in a series of sequential exposures can provide a photographic image of heat variation. The anatomical situation of the testes allows for a satisfactory degree of accuracy of measurement of heat radiation from this area.

This study reports an assessment of patients referred for infertility who have been observed to have a varicocele, and compares the pre-operative and post-operative thermograms of those patients who had a varicocele ligation undertaken; in this series the ligation was undertaken at the deep inguinal ring.

British Journal of Urology (1979), **51**, 69

Conversion Table—S.I. units

Old units			*Conversion factor multiply by:*		*S.I. units*	
Constituent	*Normal range*	*Units*	*Old to new*	*New to old*	*Normal range*	*Units*
Venous blood						
Albumin	3.5-5.5	g/100 ml	10	0.1	35-55	g/l
Bicarbonate (total)	24-30	mEq/l	1	1	24-30	mmol/l
Bilirubin	0.1-0.8	mg/100 ml	17	0.059	2-14	μmol/l
Calcium	8.6-10.5	mg/100 ml	0.25	4	2.15-2.65	mmol/l
Chloride	100-107	mEq/l	1	1	100-107	mmol/l
Cholesterol	140-240	mg/100 ml	0.026	38.5	4.0-6.5	mmol/l
Creatinine	0.6-1.4	mg/100 ml	88	0.0114	55-125	μmol/l
Glucose	65-95	mg/100 ml	0.056	18	3.5-5.5	mmol/l
Iron	110-130	μg/100 ml	0.18	5.6	circa 20	μmol/l
Magnesium	1.4-1.8	mEq/l	0.5	2	0.70-0.90	mmol/l
Phosphate	2.5-4.5	mg/100 ml	0.32	3.1	0.8-1.4	mmol/l
Potassium	3.8-5.2	mEq/l	1	1	3.8-5.2	mmol/l
Protein (total)	6.5-8.0	g/100 ml	10	0.1	65-80	g/l
P.B.I.	3.75-7.5	μg/100 ml	79	0.0127	300-600	nmol/l
IgG	500-1600	mg/100 ml	0.01	100	5.0-16.0	g/l
IgA	125-425	mg/100 ml	0.01	100	1.25-4.25	g/l
IgM	50-180	mg/100 ml	0.01	100	0.5-1.8	g/l
Sodium	136-149	mEq/l	1	1	136-149	mmol/l
Transferrin	150-300	mg/100 ml	0.01	100	1.5-3.0	g/l
Triglyceride	60-140	mg/100 ml	0.0113	88.5	M2.0 P$<$1.5	mmol/l
Uric acid	2-7	mg/100 ml	0.06	16.7	0.1-0.4	mmol/l
Urea	15-40	mg/100 ml	0.17	6.0	2.5-6.5	mmol/l
Arterial blood						
Base excess	−3-+3	mEq/l	1	1	−3-+3	mmol/l
PCO_2	32-46	mmHg	0.135	7.5	4.5-6.0	kPa
PO_2	80-100	mmHg	0.133	7.5	10.5-13.5	kPa
Urine outputs/24 h						
Calcium	200	mg	0.025	40	5	mmol
Creatinine	1-2	g	8.8	0.113	9-18	mmol
5HIAA	3-17	mg	5.23	0.19	16-90	μmol
Inorganic P.	1000	mg	0.032	31	30	mmol
Magnesium	100	mg	0.041	24	4.2	mmol
Potassium	70	mEq	1	1	70	mmol
Protein	$<$0.05	g	1	1	$<$0.05	g
Sodium	200	mEq	1	1	200	mmol
Urea	25	g	17	0.06	400	mmol
Uric acid	500	mg	0.006	167	3.0	mmol
VMA	$<$7	mg	5.05	0.2	$<$35	μmol

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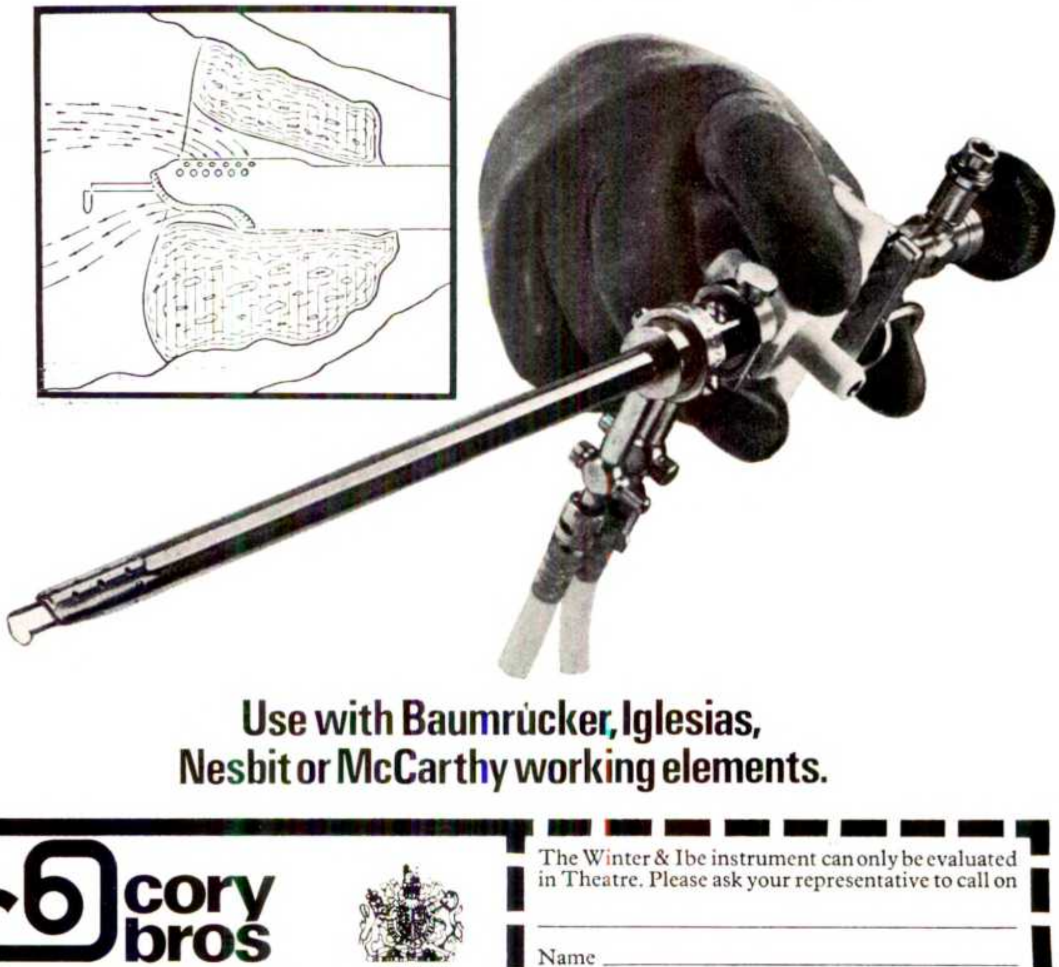

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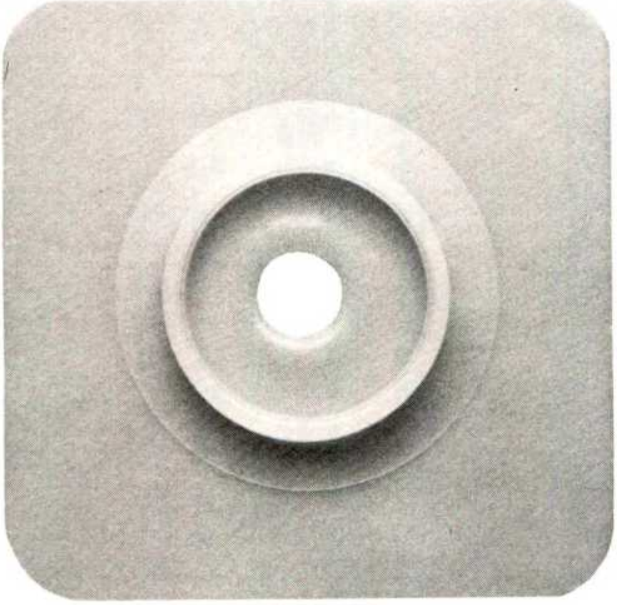

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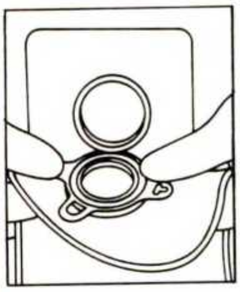

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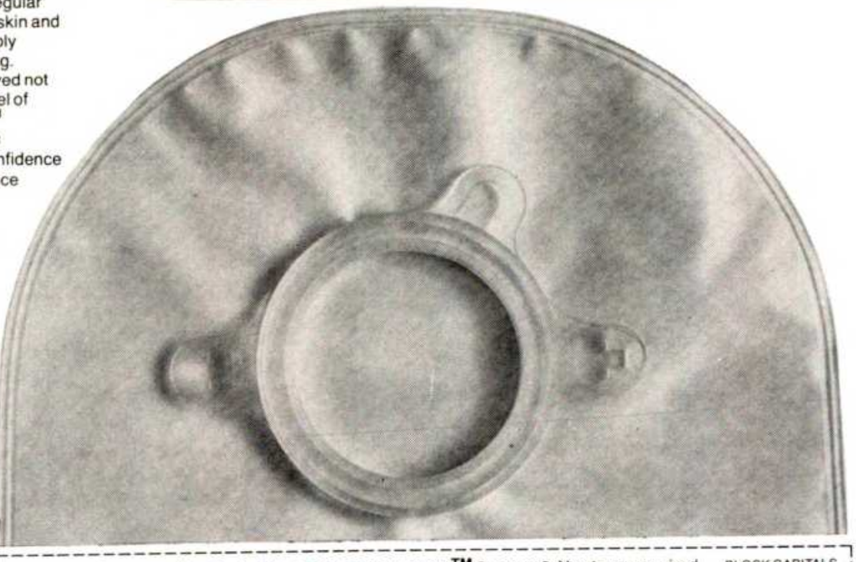

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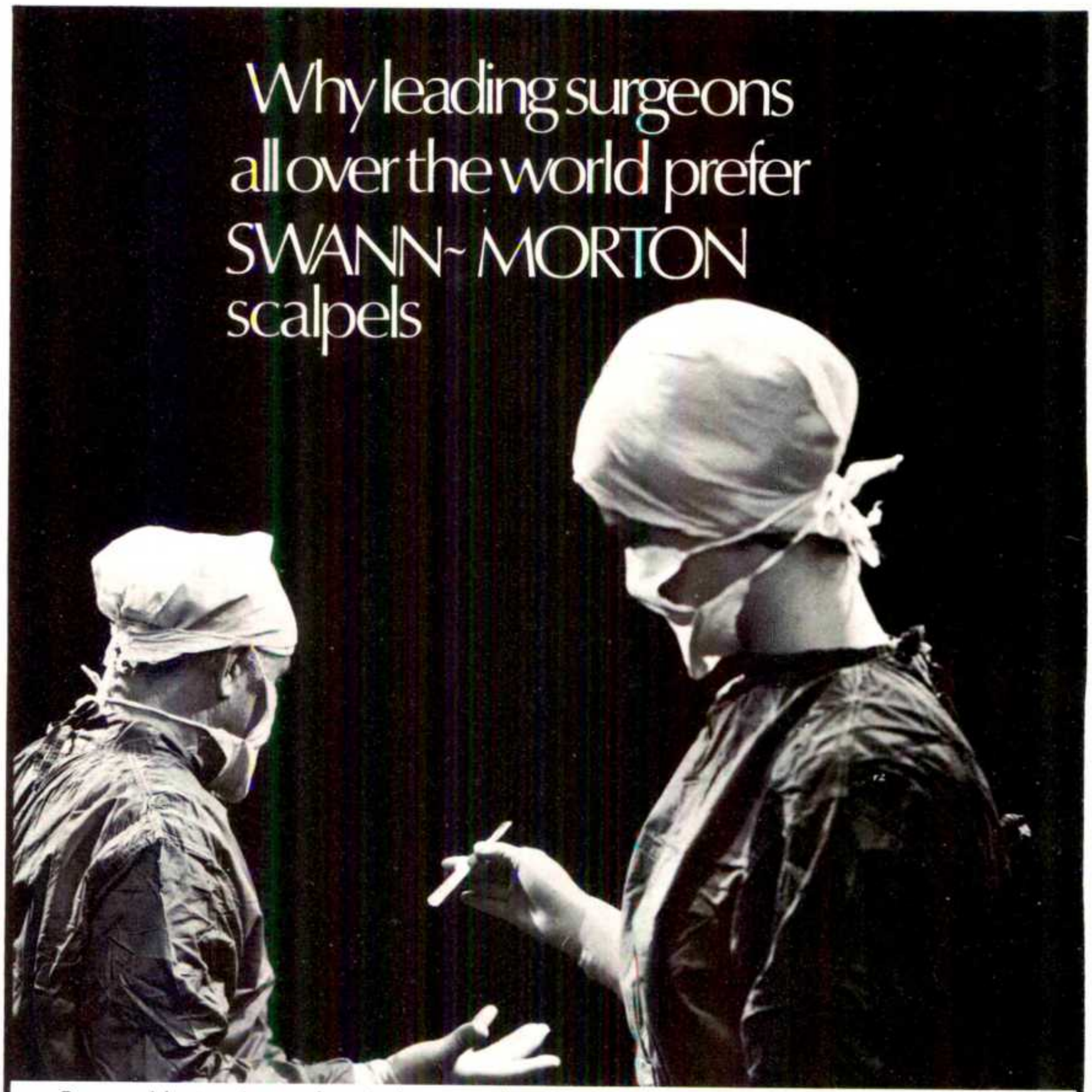

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CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal, i.e.* in anatomical order beginning with papers on the Adrenal.

A general section is included at the end.

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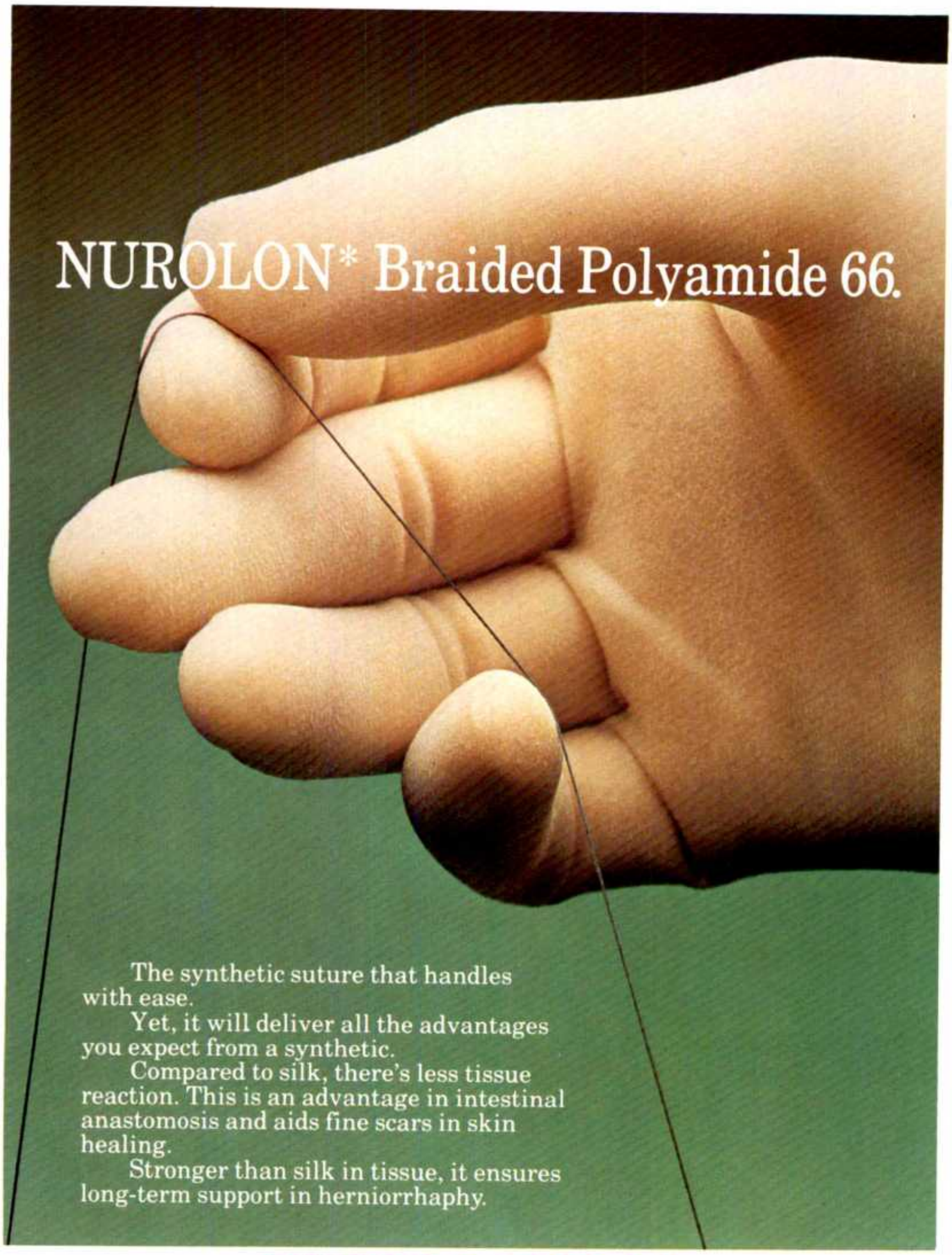

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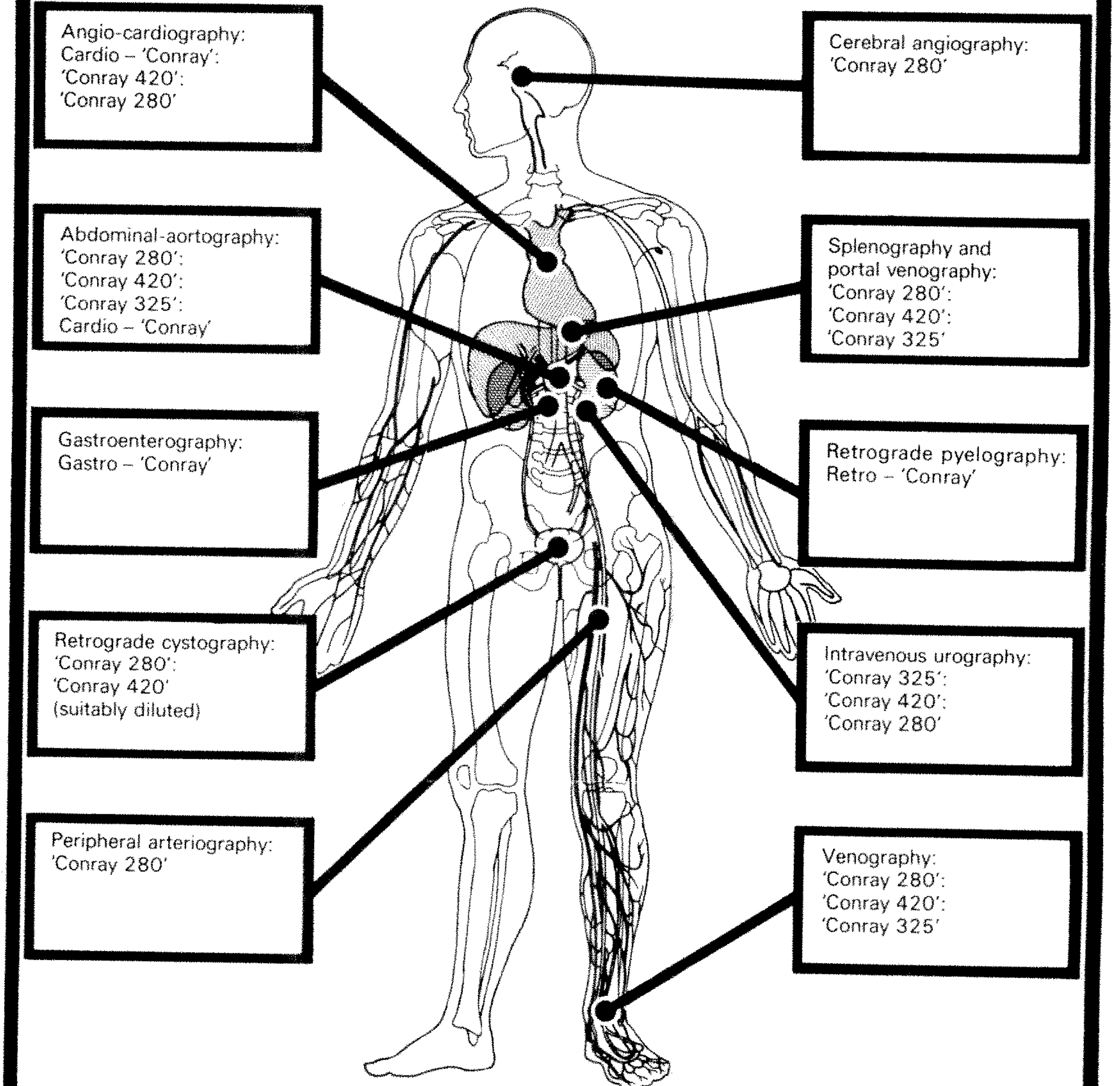

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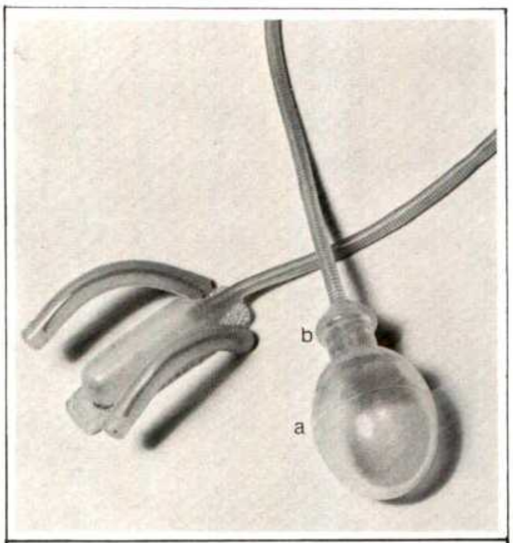

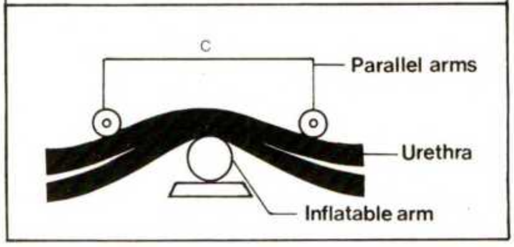

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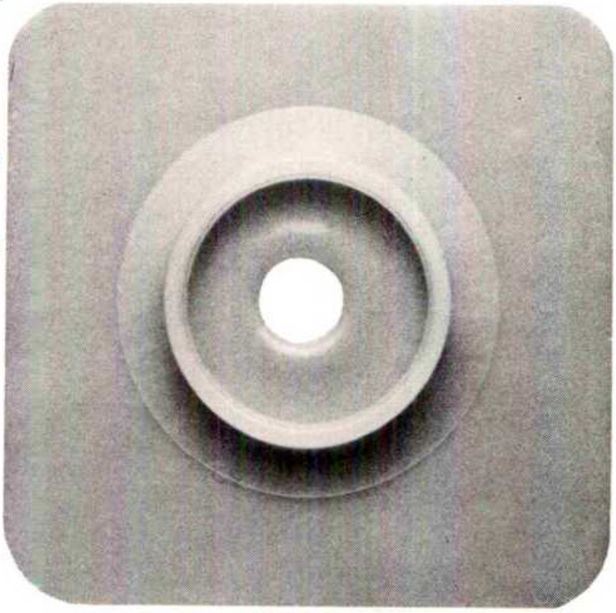

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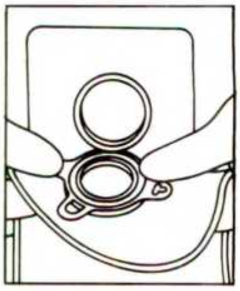

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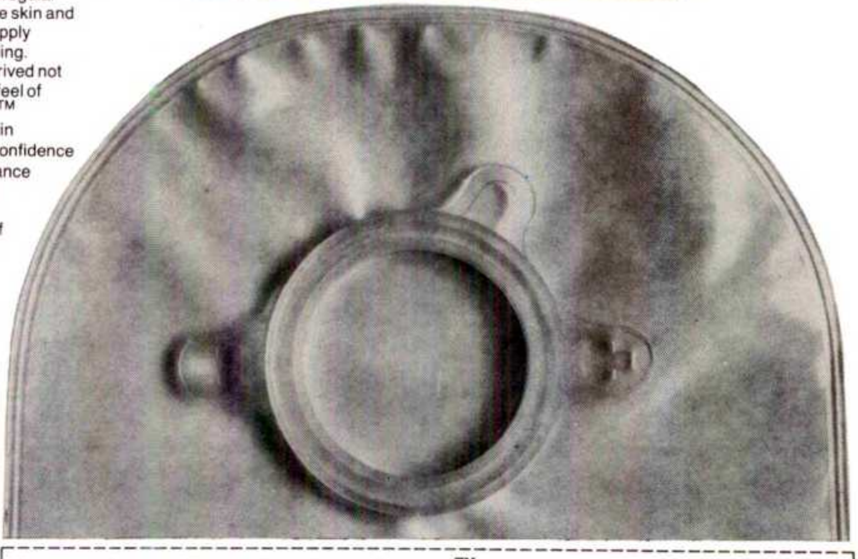

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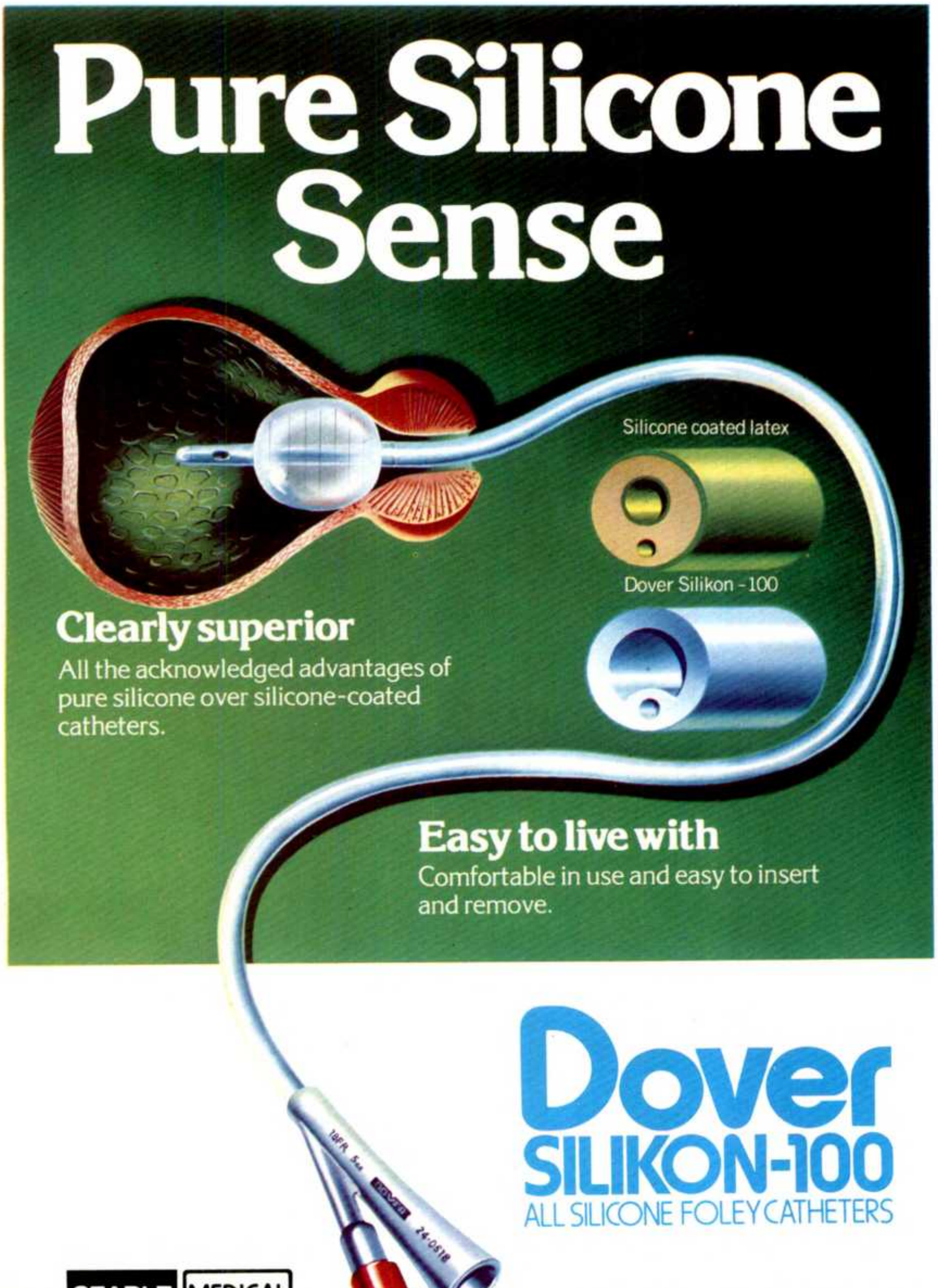

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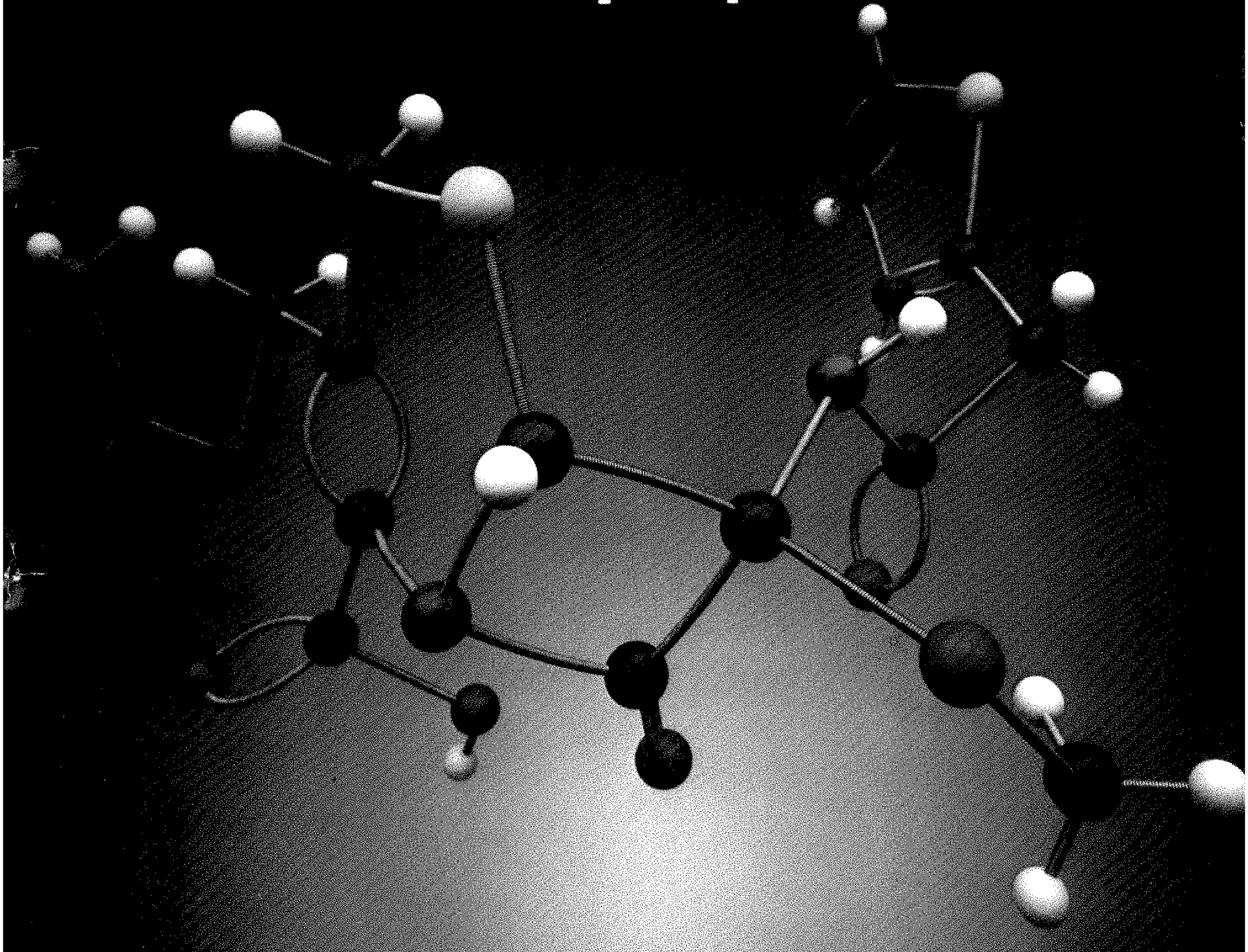

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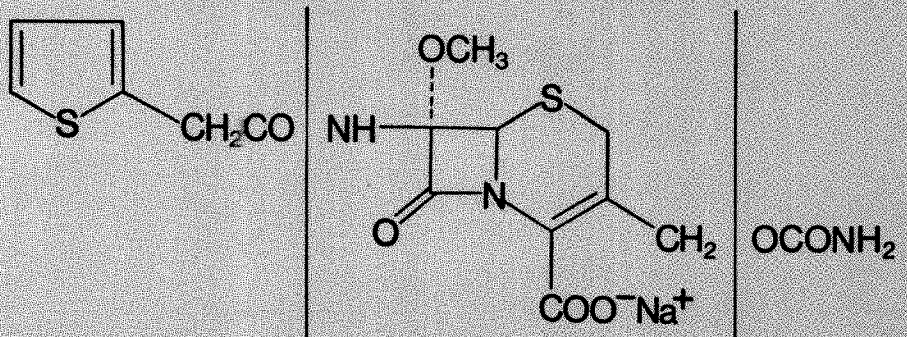

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Microbiology

'Mefoxin' is active *in vitro* against:

Aerobic bacteria

Gram-positive cocci including: Staphylococci (including coagulase-positive, coagulase-negative, and penicillinase-producing strains); Group A beta-haemolytic streptococci *(Streptococcus pyogenes)*. Group B beta-haemolytic streptococci *(Streptococcus agalactiae)*; *Streptococcus pneumoniae (Diplococcus pneumoniae)*; other streptococci (except group D streptococci including enterococci, most strains of which are resistant, e.g. *Streptococcus faecalis*) *Gram-negative cocci* including *Neisseria gonorrhoeae* (including penicillinase-producing strains), *Neisseria meningitidis*. *Gram-negative rods (facultative anaerobes)* including: *Escherichia coli, Klebsiella pneumoniae*, Klebsiella spp.; *Proteus mirabilis*. *Proteus* (indole-positive) *Proteus vulgaris, Proteus rettgeri, Proteus morganii, Haemophilus influenzae, Serratia marcescens;* Providencia spp., Salmonella and Shigella spp.

Anaerobic bacteria

Gram-positive cocci including Peptococcus spp.; Peptostreptococcus spp., Micro-aerophilic streptococcus. *Gram-positive rods including Clostridium perfringens*, Clostridium spp., Eubacterium spp., *Propionibacterium acnes. Gram-negative cocci including* Veillonella spp. *Gram-negative rods including Bacteroides fragilis, Bacteroides melaninogenicus;* Bacteroides spp. (including both penicillin-susceptible and penicillin-resistant strains); Fusobacterium spp.

'Mefoxin' is active against some strains of the following bacteria: *Acinetobacter calcoaceticus var. anitratum (Herellea vaginicola); Acinetobacter calcoaceticus* var. *lwoffi (Mima polymorpha). Alcaligenes faecalis*, Citrobacter spp. and Flavo-bacterium spp.; Enterobacter spp.

'Mefoxin' is not active against Pseudomonas, most strains of enterococci and many strains of *Enterobacter cloacae*.

Dosage and administration

'Mefoxin' may be administered intravenously or intramuscularly. (See reconstitution directions for each route below.) Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organisms, and condition of the patient.

Therapy may be started while awaiting the results of susceptibility testing.

Dosage. The usual adult dosage is 1 g or 2 g of 'Mefoxin' every eight hours. (See chart.)

In adults with renal insufficiency an initial loading dose of 1 g or 2 g may be given. After a loading dose, the following recommendations for *maintenance dosage* may be used as a guide.

Usual adult dosage

Type of infection	Dose	Frequency	Total daily dosage
Uncomplicated	1 g	Every 8 hours (occasionally every 6 hours)	3 g (4 g)
Moderately severe or severe	2 g	Every 8 hours (occasionally every 6 hours)	6 g (8 g)
Infections generally needing antibiotics in higher dosage	3 g (2 g)	Every 6 hours (Every 4 hours)	12 g

Maintenance dosage of 'Mefoxin' in adults with reduced renal function

Renal function	Creatinine clearance (ml/min)	Dose	Frequency
Mild impairment	50-30	1-2 g	Every 8-12 hours
Moderate impairment	29-10	1-2 g	Every 12-24 hours
Severe impairment	9-5	0.5-1 g	Every 12-24 hours
Essentially no function	<5	0.5-1 g	Every 24-48 hours

In the patients undergoing haemodialysis, the loading dose of 1 to 2 g should be given after each haemodialysis, and the maintenance dose should be given as indicated in the table above.

Intravenous administration: reconstitute 'Mefoxin' with Water for Injection BP. 1 g is soluble in 2 ml. Although 'Mefoxin' is very soluble, for intravenous use it is preferable to add 10 ml of Water for Injection BP to the 1 g vial or the 2 g vial. Shake to dissolve and then withdraw entire contents of vial into syringe.

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Skin and soft tissue infections
Bone and joint infections
Urinary tract infections
Respiratory tract infections (e.g. inhalation pneumonia)

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Mefoxin is exceptionally valuable wherever Gram-negative pathogens
nd anaerobes are involved in mixed infections. When mixed
fections are suspected, therapy may be started while awaiting the
esults of susceptibility testing.

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INJECTION

First of the cephamycins

the vein over a period of 3 to 5 minutes or may be given through the tubing when the patient is receiving parenteral solutions.

An intermittent intravenous infusion of 'Mefoxin' may be employed when large amounts of fluid are to be given. However, during infusion of the solution containing 'Mefoxin', it may be advisable temporarily to discontinue administration of any other infusion solution at the same site (by using an appropriate IV infusion set).

A solution of 'Mefoxin' may also be given by continuous intravenous infusion (see below for compatibility and stability).

Intramuscular administration ONLY
Reconstitute 'Mefoxin' 1 g with 2 ml of Water for Injection BP, or 0.5% or 1% lignocaine hydrochloride (without adrenaline) solution. 'Mefoxin' is given by deep injection into a large muscle mass. Avoid injection into a blood vessel.

Compatibility and stability
A solution of 'Mefoxin' in Water for Injection BP may be added to the following solutions: 0.9% Sodium Chloride Injection BP, 5% or 10% Dextrose Injection BP, Dextrose and Sodium Chloride Injection (5%/0.9%, 5%/0.45%, or 4.3%/0.18%), Lactated Ringer's Injection USP, 5% Dextrose in Lactated Ringer's Injection, 5% or 10% invert sugar in water, 10% invert sugar in saline solution, 4.2% Sodium Bicarbonate Injection BP, M/6 Sodium Lactate Injection BP.

'Mefoxin', as constituted to 1 g/10 ml with Water for Injection BP, Water for Injection BP preserved with parabens or benzyl alcohol, 0.9% Sodium Chloride Injection BP, or 5% Dextrose Injection BP, maintains satisfactory potency for 24 hours at room temperature, for [illegible] hours under refrigeration, and for 13 weeks in the frozen state.

'Mefoxin' can be administered concomitantly with such antibiotics as gentamicin, tobramycin, carbenicillin or amikacin. When 'Mefoxin' is administered with another antibiotic, they should not be mixed in the same syringe.

Contra-indications
'Mefoxin' is contra-indicated in persons who have shown hypersensitivity to cefoxitin. In the absence of clinical experience 'Mefoxin' should not be administered to patients who have shown hypersensitivity to cephalosporins.

Precautions
There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and other β-lactam antibiotics, penicillins, and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most β-lactam antibiotics.

Before therapy with 'Mefoxin', careful inquiry should be made concerning previous hypersensitivity reactions to β-lactam antibiotics. 'Mefoxin' should be given cautiously to penicillin-allergic patients.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. If an allergic reaction to 'Mefoxin' occurs, the drug should be discontinued.

The total daily dosage should be reduced when 'Mefoxin' is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see 'Dosage and administration') because high and prolonged serum antibiotic concentrations can occur from usual doses.

Interference with laboratory tests
A false-positive reaction to glucose in the urine may occur with reducing substances but not with the use of specific glucose oxidase methods.

Use in pregnancy
Use of the drug in women of childbearing potential requires that the anticipated benefits be weighed against possible hazards. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the foetus due to 'Mefoxin'. There are no controlled studies with 'Mefoxin' in pregnant women.

Nursing mothers
'Mefoxin' is excreted in human milk.

Infants and children
Pending the outcome of clinical trials in progress, the conditions for use of 'Mefoxin' in infants and children remain to be defined.

Side effects
'Mefoxin' is generally well tolerated. Side effects rarely require stopping treatment and usually have been mild and transient.

Local reactions
Thrombophlebitis has occurred with intravenous administration. Pain induration and tenderness after intramuscular injections have been reported.

Allergic
Maculopapular rash, urticaria, pruritus, eosinophilia, fever and other allergic reactions have been noted rarely.

Gastro-intestinal
Diarrhoea has been reported rarely.

Blood
Transient leucopenia and neutropenia have been reported. Some individuals, particularly those with azotaemia, may develop positive direct Coombs tests during therapy with 'Mefoxin'.

Liver function
Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase have been reported rarely.

Kidney
Elevations in serum creatinine and/or blood urea levels have been observed. The role of 'Mefoxin' in changes in renal function test is difficult to assess, since factors predisposing to pre-renal azotaemia or to impaired renal function usually have been present.

Presentation
In vials containing 1 g or 2 g of cefoxitin as the sodium salt. Each gram of cefoxitin contains approximately 51.5 mg (2.2 mEq) sodium.

Product licence numbers: 1 g, 0025/0130; 2 g, 0025/0131

Product authorisation numbers: 1 g, PA 35/42/1; 2 g, PA 35/42/2

Issued October 1978

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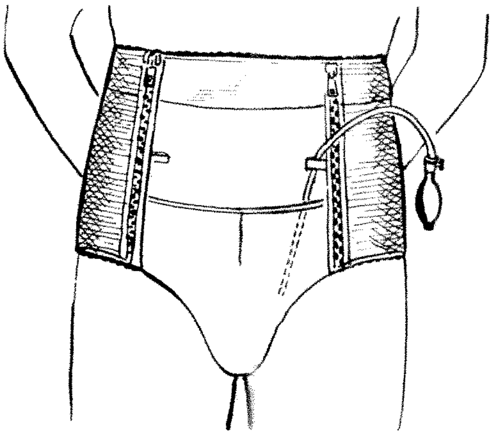

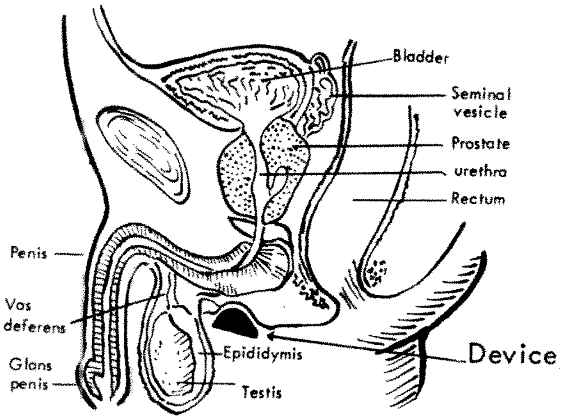

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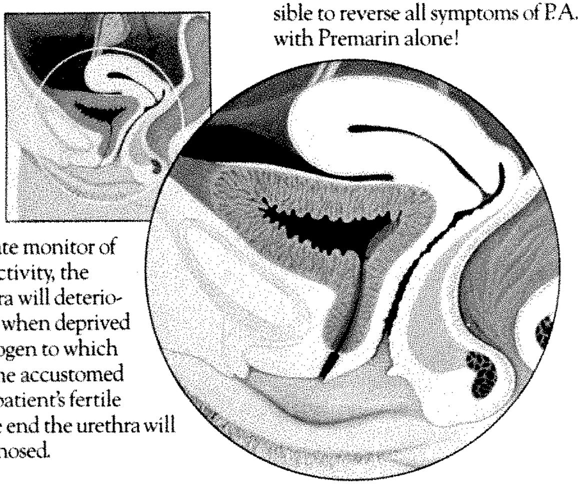
Untreated, these atrophic changes can be devastating and demoralising in their effect.[2]



A delicate monitor of oestrogen activity, the distal urethra will deteriorate rapidly when deprived of the oestrogen to which it has become accustomed during the patient's fertile years. In the end the urethra will become stenosed.

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4. If treatment is instigated in the early stages of this disorder – for instance within the first six/twelve months of symptoms – it may be possible to reverse all symptoms of P.A.U. with Premarin alone!

However in patients with a longer history of frequency and urgency, if oestrogen therapy does not effect a rapid and complete elimination of symptoms then the possibility of a secondary urethral stenosis should be considered.

References:

1. Willington, F. L. The Practitioner. 220, 739, 1978.
2. Smith, P. J. B., Ayerst Medical Library Vol. 2, No 2, 1978.
3. Smith, P. J. B., The Practitioner, 218, 97, 1977.

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Contra-Indications: Uterine myomatosis. Endometriosis. Cancer of the breast and uterus. Active hepatic, renal and severe cardiac disease. Undiagnosed genital bleeding. Diabetes. Thyrotoxicosis. Pregnancy. Personal history of thrombosis.

Precautions
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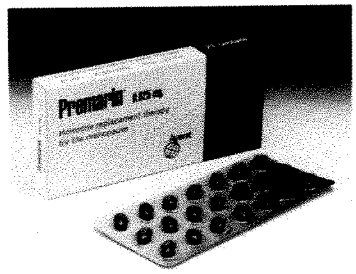

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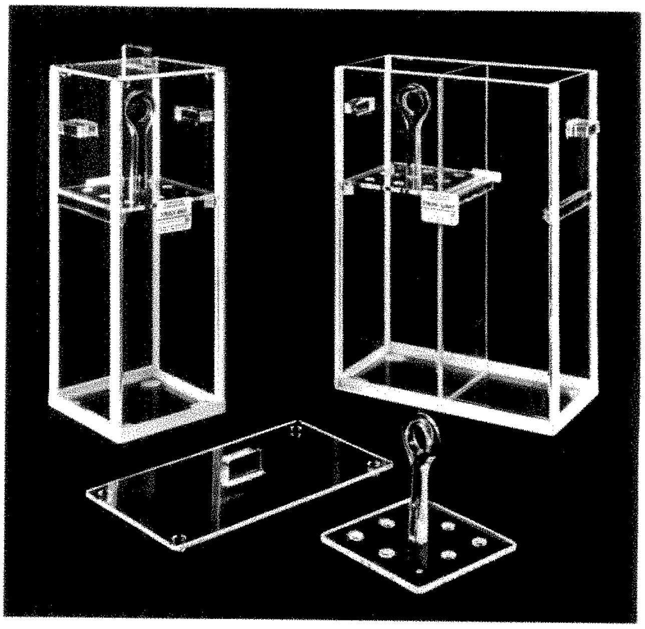

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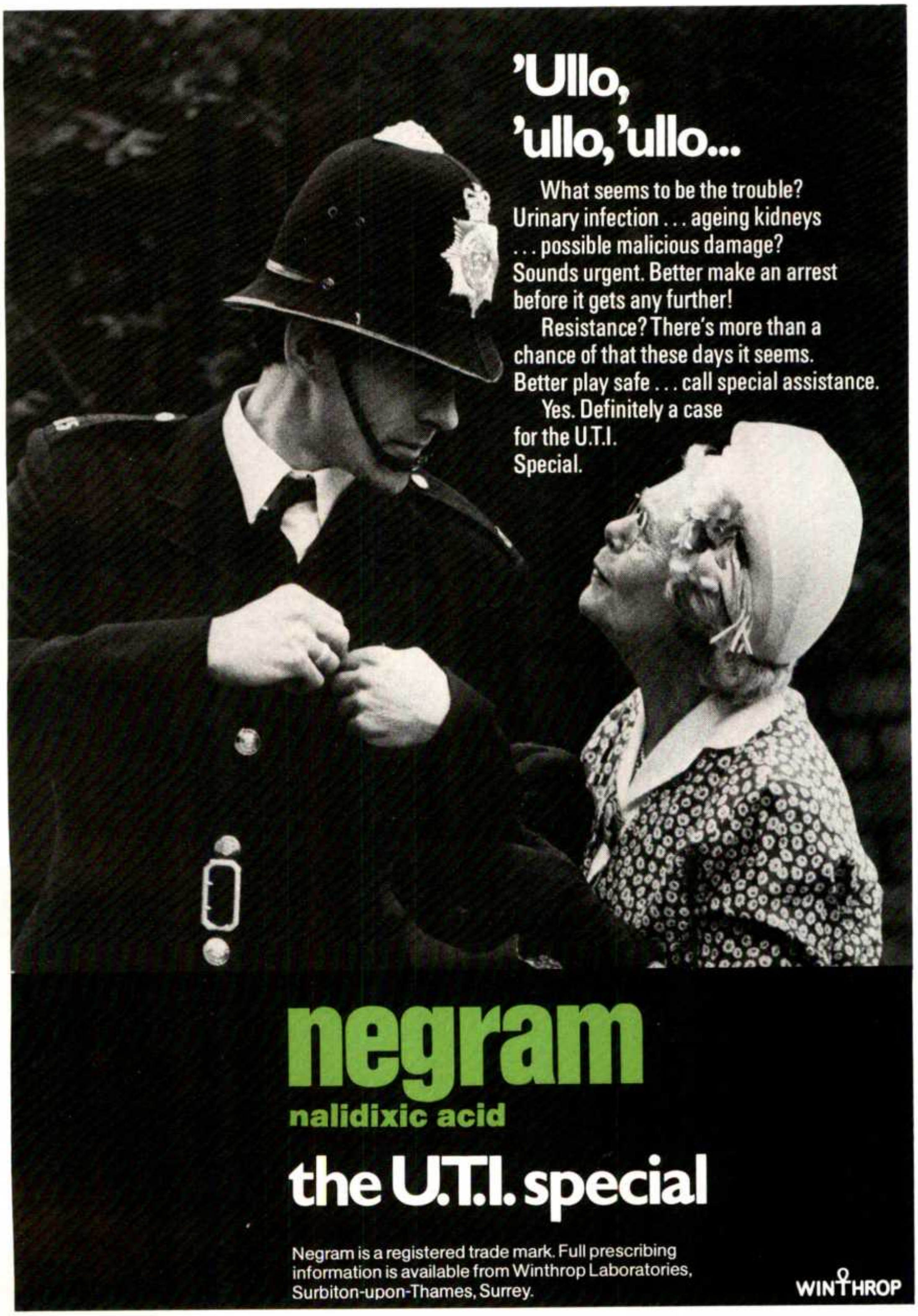

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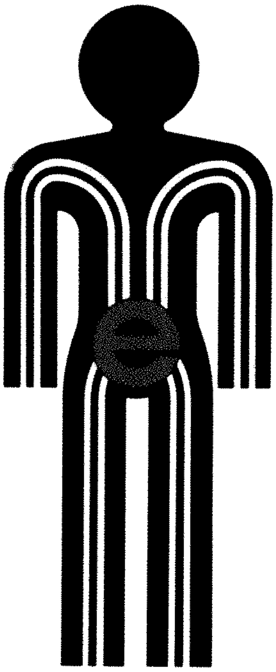

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References
1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., 49, 73-79. 2. Mayer. E.J. Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, 32, 114-119. 3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., 111: 231-238. 4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

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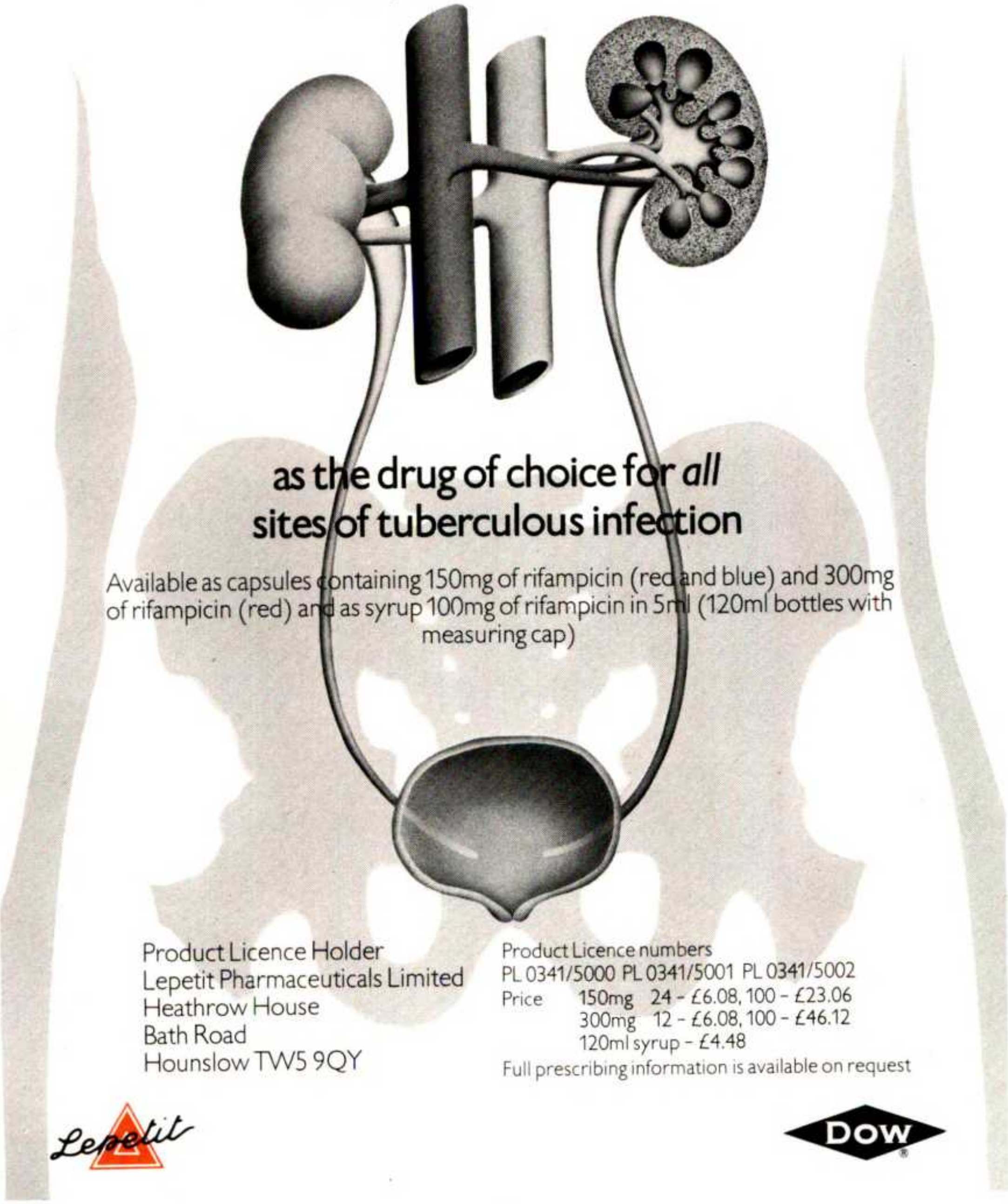

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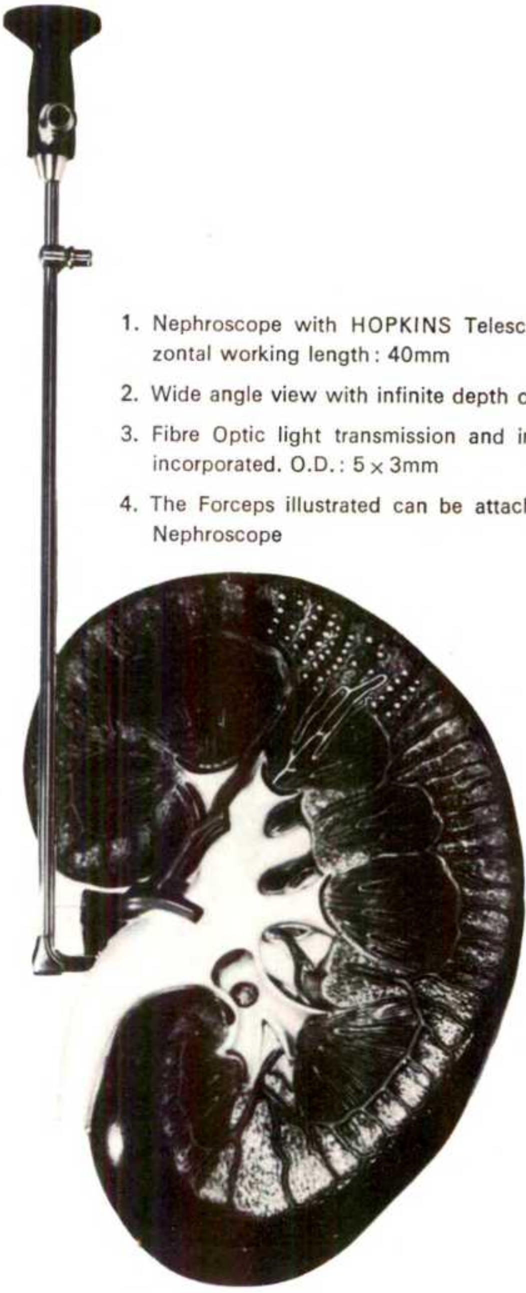

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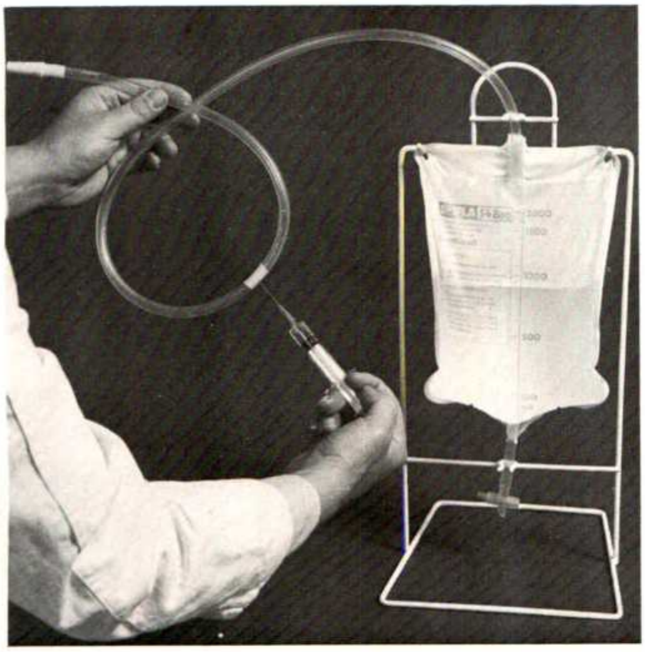

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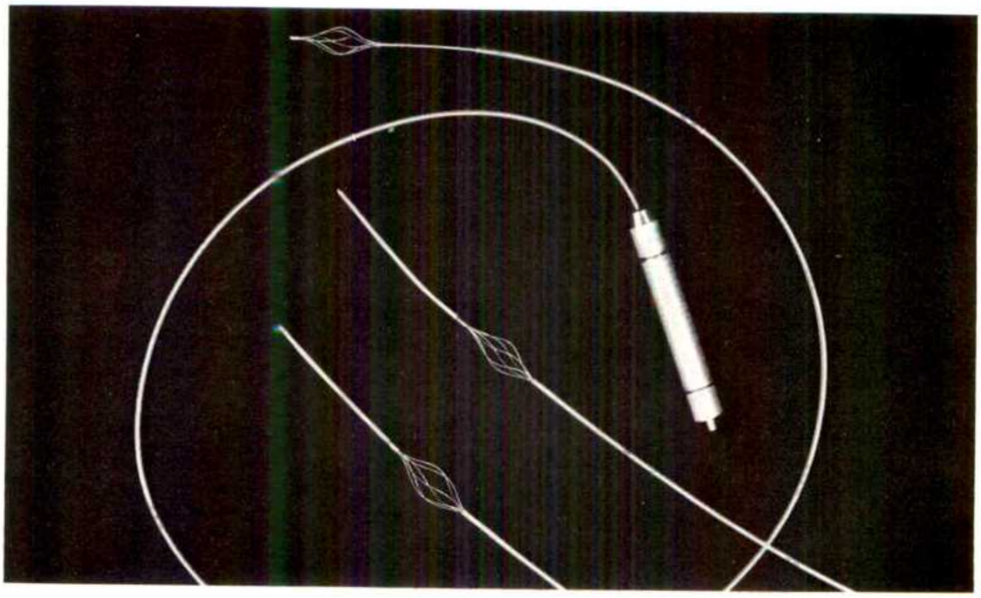

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British Journal of Urology (1979), **51**, 73-77

Genetic Associations of Transitional Cell Carcinoma

D. W. HERRING, R. A. CARTWRIGHT and D. D. R. WILLIAMS

Department of Surgery, Dryburn Hospital, Durham; Yorkshire Regional Cancer Organisation, Cookridge Hospital, Leeds; Department of Anthropology, University of Durham, Durham

Summary—A series of 101 cases of transitional cell carcinoma (TCC) was contrasted with a control series for several genetic parameters. Three genetic associations were demonstrated with the TCC patients having A gene frequencies, HLA B5 and HLA CW4 genes all higher than might be expected by chance. A classification of the natural history of the disease is used to show that the HLA frequencies vary with the more or the less severe forms of the disease.

Transitional cell carcinoma of the urothelium has well-described environmental causes related to the dyeing and rubber industries (Case *et al.*, 1954; Case, 1966; Case, 1969) and to smoking cigarettes (Hoover and Cole, 1971). However, not all people subjected to these environmental stimuli develop the disease, while a few who do develop TCC have never smoked or had industrial contact with the appropriate carcinogens.

This paper is concerned with the possibility that individual genetic variability influences the appearance of the disease and contributes to the differing natural histories seen in TCC. The best understood attributes of individual variability are inherited factors such as blood groups. The general relationships between such factors and disease have been reviewed by Mourant (1976). Individual variability is particularly relevant in cancer studies in that immune competence, in the recognition of cell surfaces, is suppressed in such diseases. Human cell surface variability is measured, to a certain degree, by red and white cell groups.

The results do not depend on the use of genetics in the classical sense and although there have been 3 reports showing familial transmission of TCC (Fraumeni and Thomas, 1967; McCullough *et al.*, 1975; Sharma *et al.*, 1976), it is unlikely that the disease is commonly a unifactorially inherited attribute. This paper attempts to indicate how improved identification of those at risk in the community might take place.

Patients and Methods

All patients treated by surgeons in the Durham Hospital Area over the last 5 years were identified and contact was attempted with all living patients when they presented to the hospital for routine review, or they were asked by letter to attend an out-patient session.

Each patient was asked for his address and occupation and for details of any change in each. A record was also made of sex, age, smoking habits and family history of bladder disease and other diseases. This was supplemented in each case by information from the notes on the site of the tumour, its histology and staging and the action taken at the first and each subsequent cystoscopies. Finally a blood sample was taken for analysis.

The red blood cells were grouped for a variety of antigens including the ABO system, whilst the white cells were typed for a range of HLA specificities using the NIH method.

A control group was assembled having about 2 controls for each case matched for social class, within 3 years of the age of the propositi and from the same village. The controls were not matched for sex. The control group comprised either trauma patients with no other known pathology or the neighbours of diabetics used originally in another study. Blood from the controls was analysed in the same way as that from the disease group.

The characteristics of the TCC were defined by cystoscopy and on a broad histopathological basis. The grading of the tumour was recorded using the standard TNM classification.

An important aspect of this study was to see

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if the natural history of the disease (incorporating interventional treatments), as measured by repeated cystoscopies, is influenced by individual genetic variation. An attempt has been made to measure this by devising an artificial classification reflecting the varying invasiveness and aggressiveness of TCC. Patients who had at least 3 cystoscopies and who had been under review for at least 6 months were incorporated into this part of the study. Each patient was grouped into one of the following types:

Type A	These patients had 1 to 3 well differentiated carcinomas with no recurrence or few recurrences over at least 6 months. The carcinomas were either sessile or papillary in configuration. These were mainly T1 grade at first cystoscopy.
Type B	These patients had more than 3 carcinomas and/or more than 3 recurrences. The disease took longer to settle down. These tumours were either T1 or T2 at first cystoscopy.
Type C	These patients had tumours which started off as type A or B but which became more aggressive over the first year of follow-up. More commonly these were patients who presented with deeply invasive tumours or spread beyond the urothelium.

All data were computerised and the analyses performed using the Northern Universities Multiple Access Computer, an IBM 370/137.

Results

One hundred and five patients were eligible for the study in that they were alive between September and December 1976. Four refused to participate, leaving a sample of 101 which was contrasted with 207 controls (Table 1). The mean age at presentation was 52.25 years, with a standard deviation of 12.10.

Table 1 The Contrast between the Control and Patient Samples which shows no Statistical Difference between the Groups

	TCC	*Control*
Mean age (years)	63.83	63.55
Standard deviation	11.09	11.45
Range (years)	37-86	35-89
Males (%)	73.50	42.50

Table 2 The TNM Staging Based on the Biopsy Results from the First Cystoscopy Showing Absolute Numbers and the Percentages for each Sex in Brackets

	Males	*Females*
T1	39 (56.6)	15 (62.5)
T2	18 (26.1)	3 (12.5)
T3	9 (13.0)	5 (20.8)
T4	3 (4.4)	1 (4.2)

The tumours were mainly sited in the bladder except for 2 from the ureter and 3 in the urethra. The staging at first cystoscopy is shown in Table 2. There was no significant sex difference (χ^2 0.23 for males v. females, T1 v. rest, $P>0.5$).

The duration of the disease from the occasion of the first cystoscopy until January 1977 is given in Table 3. The range in this cross-sectional sample is considerable, being from 1 month to 16 years, the mean duration being 3.3 years. Table 3 also contrasts spread with the duration of the disease.

Consideration was given to the ABO blood groups in patients presenting with TCC, contrasting the findings with the matched control group. Detailed results are given in Table 4 and these indicate a statistically significant increase in blood group A in TCC patients.

HLA typing of the sample group with TCC and the control group was undertaken. The results are given in Table 5 where they are also contrasted with the results of Terasaki *et al.* (1977). These results, together with the results given in Table 4, are statistically homogenous for sex. Contrasting the disease and control groups in Table 5 by a series of chi-squared tests (2 × 2) showed 2 significant results which are asterisked. No correction was made for the number of chi-square tests per-

Table 3 Tumour Spread and the Duration of Disease from First Cystoscopy until January 1977; the Numbers of Cases are given Under Each Heading

	T1	*T2*	*T3*	*T4*
Under 1 year	10	4	3	2
1-2 years	5	4	4	2
2-3 years	8	3	1	-
3-4 years	4	3	2	-
Over 4 years	23	5	2	-

Table 4 ABO Blood Groups in TCC Patients and Controls: Total Numbers and their Percentage Frequencies are given in Brackets

	A_1	A_2	A_1+A_2	B	A_1B	O	*Totals*
TCC	37 (36.6)	12 (11.9)	49 (48.5)	6 (5.9)	5 (5.0)	41 (40.6)	101
Control	64 (31.1)	13 (6.3)	77 (37.4)	20 (9.7)	6 (2.9)	103 (50.0)	206

The chi-squared test contrasting the aggregated groups A and Ab with O and B gives a significant value of 4.84, $P=0.02$-0.05 for 1 d.f.

formed. The chi-square value for the significantly increased frequency of HLA-B5 amongst TCC patients is 4.46 and that for HLA-CW4 is 4.70. The sample sizes in Table 5 are 101 for the TCC group, and as some were not HLA tested, 202 for the controls and 264 for the Californian series of Terasaki *et al.* (1977), unless otherwise stated.

The natural histories of the diseased group, incorporating interventional treatment, in ABO and HLA types were then classified into types A, B or C as previously defined. The results are shown in Table 6. Some specificities have been omitted because of small subsample sizes. The table gives the percentage frequencies of the phenotypes. It was not possible to classify all the TCC sample into these types. The sex ratio of the 3 natural history subgroups is of interest in that type A, the least aggressive group, incorporates 36 males (87.8%) while the other 2 types have more females (55.2 and 72.7% males respectively in types B and C). It is impossible to establish if these are significant differences because of small samples. However, there are apparently considerable genetic differences between the 3 groups.

Table 5 HLA Types in TCC Patients and Controls and TCC Patients from California

	TCC		*Control*		*Terasaki* et al. *(1977)* *(%)*
	N	*(%)*	*N*	*(%)*	
HLA antigens					
HLA A1	29	28.7	75	37.1	25
2	52	51.5	82	40.6	45
3	30	29.7	61	30.2	30
9	18	17.8	24	11.9	22
10	16	15.8	28	13.9	14
11	7	6.9	18	8.9	11
* HLA B5	19	18.8	19	9.4	9
7	28	27.7	53	26.2	28
8	20	19.8	62	30.7	17
12	35	34.7	74	36.6	26
13	6	5.9	8	3.9	6
14	7	6.9	18	13.9	9
27	7	6.9	16	7.9	9
W15	15	† 14.9	19	9.4	8
W17	9	8.9	14	6.9	10
**HLA CW4	23	‡ 23.0	24	† †12.3	-

† Sample of 95, ‡ sample of 100, † † sample of 195.
* χ^2 5.37 with 1 d.f. and $P=0.02$-0.05.
** χ^2 5.52 with 1 d.f. and $P=0.01$-0.02.

The numbers and percentages are those who respond positively to the appropriate antisera out of the total number tested with that particular specificity.

Discussion

Transitional cell carcinoma is a complex disease. The role of environmental carcinogens has been extensively studied but clearly the host response plays an important part not only in the acquisition of the disease but also in the progress of the disease once acquired. This paper deals in the main with the relationship between the natural

Table 6 The Natural History Typology Contrasted with the ABO and HLA Blood Groupings

	Type A	*Type B*	*Type C*
ABO phenotypes			
0	43.9	37.9	45.5
A_1+A_2	46.3	44.8	47.5
B	7.3	10.3	-
HLA phenotypes			
A1	16.1	21.7	24.2
2	30.7	28.3	39.4
3	19.4	21.7	18.2
9	11.3	15.2	9.1
10	12.9	8.7	9.1
11	6.5	4.4	-
B5	14.1	11.4	13.3
7	12.5	25.0	26.7
8	12.5	18.2	10.0
12	12.5	22.7	30.0
W15	14.1	9.1	3.3
W17	10.9	4.6	-
CW4	21.9	32.1	22.7
Totals	41	29	22

The results are given as percentages of the number of cases positive to the appropriate antisera.

history of TCC and gene frequency occurrence in patients acquiring the disease, having contrasted these patients with a matched control population.

For such studies the control population is important in its composition and great care has been exercised in grouping the controls for age, social class and geographical location. The reason for this is partly because ABO and possibly HLA gene frequencies vary for these factors in this country and partly because the study is a small one. This is compensated to some degree by the fact that the study includes nearly all the cases known in the area. The results of the control population contrast favourably with existing gene frequency data from the North of England (Kopéc, 1970; Murray *et al.*, 1976) in that chi-squared comparisons show no statistical differences between the samples.

The ABO results presented here show that the TCC group has an increased frequency of the A gene contrasted with the control population. This is not a new finding; Vogel and Krüger (1968) and others have reported a general bias to the A gene in many types of cancer including TCC. They showed for TCC that the A:O ratio for several combined studies was 1.26, although there was significant heterogeneity amongst the various series. The A:O ratio for the present study is 1.20. The largest comparable European series is by Dick *et al.* (1962) with a sample of 558; this series had an A:O ratio of 1.38. This was a German series, however, where the A gene is naturally more common.

The HLA series shows 2 genetic associations with TCC. At the B locus there is an excess of the B5 antigen and at the C locus there is an excess of the CW4 factor. There is only one major series of HLA types in cancer reported by Terasaki *et al.* (1977) and among other data this paper gives the results of 264 bladder cancer patients. The data are given in Table 5. These Californian results are difficult to contrast with the present study because of the biological diversity of the American population and the lack of detail on the techniques of sample and control collection. The study showed a weak association between HLA BW35 and TCC and no association with HLA B5, while HLA CW4 was not tested for. The associations found in this report are thus unreported hitherto. The link with HLA CW4 might be due to the fact that this gene is in linkage disequilibrium with HLA BW35, a specificity not tested for in our study.

The relative incidence for the HLA associations are 2.23 and 2.13 for HLA B5 and HLA CW4 respectively. The combined risks for HLA B5, HLA CW4 and the ABO A gene together are much greater; for example, the risk of getting TCC in a person who is ABO A, HLA B5 and HLA CW4 is over 15 times the mean population risk.

The mechanistic basis for these genetic associations is still obscure, in particular for the ABO system. There are some pointers for the HLA system, however. A reduced T-lymphocyte response in patients with TCC has been reported by Catalona *et al.* (1974). Such responses may be controlled by the immune response genes located very close to the HLA loci on chromosome 6, as suggested by Nerup *et al.* (1976).

It is necessary to perform many chi-squared tests to assess the results and one might expect some tests to be significant by chance. However, 3 significant tests out of 17 are greater than one might expect fortuitously and the results are likely to be statistically valid.

The classification of the natural history of the disease is manifestly an artificial aggregation of an infinitely varying disease. Inevitably, some types classed as A or B will, in time, become B or C and so the dynamic nature of the disease is still partially obscured. The overall picture gained from this exercise is useful. It points to the fact that there appear to be different genes involved with the more and the less severe forms of the disease. It might be significant in this respect that the genes which appear to differ with respect to disease course are not the ones which are associated with acquiring the disease in the first instance. Perhaps 2 mechanisms are involved here: those genes which determine susceptibility to TCC and those genes that influence the natural response to the neoplastic process.

This is a preliminary study designed along the lines suggested by Emery (1976) to see if further work is justified. Now it would seem appropriate to find corroboration using larger series and a prospective study designed to monitor the natural history of the disease.

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The Value of Large Volume Selective Arteriophlebography of the Renal Veins in the Pre-Operative Assessment of Renal Carcinoma

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Summary—The accuracy of large volume selective arteriophlebography in demonstrating the main renal veins in 28 patients with renal carcinoma is presented. The diagnosis was shown to be correct at operation in 96% of examinations.

It is suggested that the technique is valuable and safe and should form part of the routine pre-operative assessment of patients with renal carcinoma.

The presence of renal vein thrombosis in renal carcinoma not only adversely affects the prognosis but influences the approach used for nephrectomy.

As venous catheterisation may disseminate tumour thrombus (Lang, 1971) we do not use selective renal phlebography for the assessment of patients with renal carcinoma, preferring the indirect method described here.

Conventional selective angiography using 8 to 12 ml of 45 to 60% contrast medium rarely demonstrates the renal veins adequately because of dilution by the renal circulation. This dilution effect can be overcome if a sufficiently large volume of contrast medium is used (Henriksson and Mikaelsson, 1973).

This paper assesses the value of large volume selective renal arteriography with follow-through as a method of demonstrating the renal veins in renal carcinoma. This technique we have called arteriophlebography.

Material and Methods

Twenty-eight patients, 17 male and 11 female, aged 38 to 72 years (mean 58 years) were investigated by large volume selective arteriophlebography.

The tumour involved the right kidney in 13 patients and the left kidney in 15 patients.

Thirteen of the 28 patients were shown on excretion urography to have tumours involving the renal pelvis.

All the patients were subsequently shown at nephrectomy to have renal carcinoma.

The patient was placed in the supine position on a serial film changer. A mid-stream aortogram to include both kidneys was first obtained using the percutaneous perfemoral catheter technique. An 8 FG selective femoro-renal arterial catheter was then introduced into the renal artery. If the mass being investigated was clearly shown on the flood examination to be a carcinoma, large volume selective arteriophlebography was then performed. If there was doubt, this was preceded by a conventional small volume investigation.

For the selective studies the radiographic field was sufficiently wide to include the renal mass, the full length of the renal vein being studied and the adjacent inferior vena cava. A control film was exposed for subtraction purposes.

Fifty millilitres of meglumine iothalamate 60% were injected by hand as rapidly as possible. Injection and filming were started simultaneously. Films were exposed at the rate of 3 per sec for 4 sec followed by 1 every 2 sec to cover a total of 25 sec.

No complications from this technique were encountered in this series.

Results

The main renal vein was shown to be free of malignant thrombus in 20 of the 28 arteriophlebograms and this was confirmed at operation.

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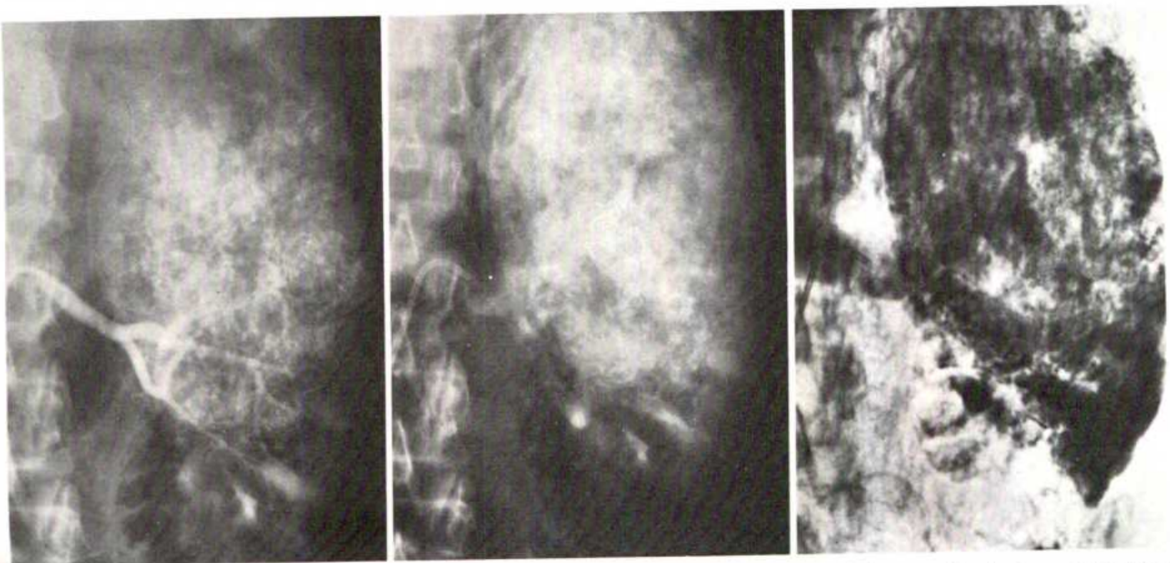

Fig. 1 (a) Arterial phase. (b) Venous phase. (c) Subtraction film. The patent left renal vein is most clearly demonstrated in the subtraction film.

In 7 of the examinations the main renal vein was not demonstrated angiographically and tumour thrombus was found at nephrectomy. In one examination the renal vein could not be identified on the angiogram but was found to be normal at operation.

Collateral veins were demonstrated in 4 of the examinations in which the renal vein was normal and in all 7 of the examinations where the main renal vein contained tumour thrombus.

No collateral veins were demonstrated in the examination in which the renal vein was incorrectly diagnosed as thrombosed.

Thus the absence of tumour thrombus was

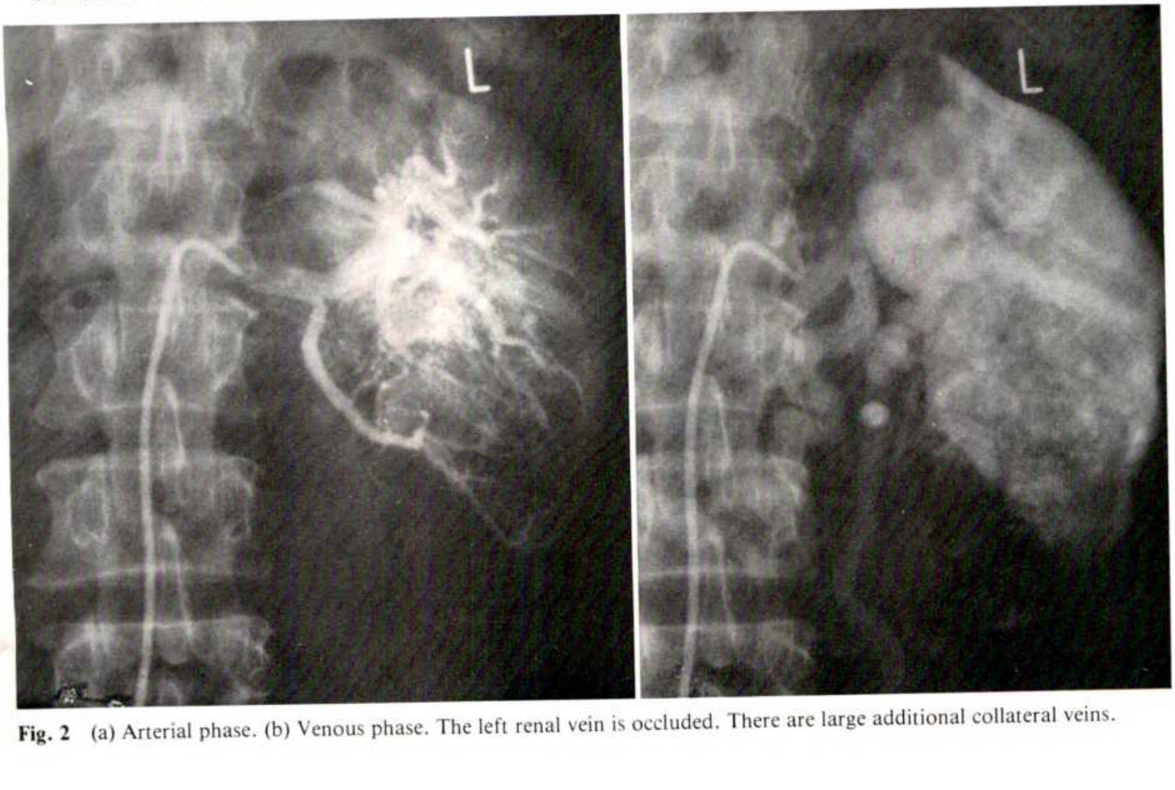

Fig. 2 (a) Arterial phase. (b) Venous phase. The left renal vein is occluded. There are large additional collateral veins.

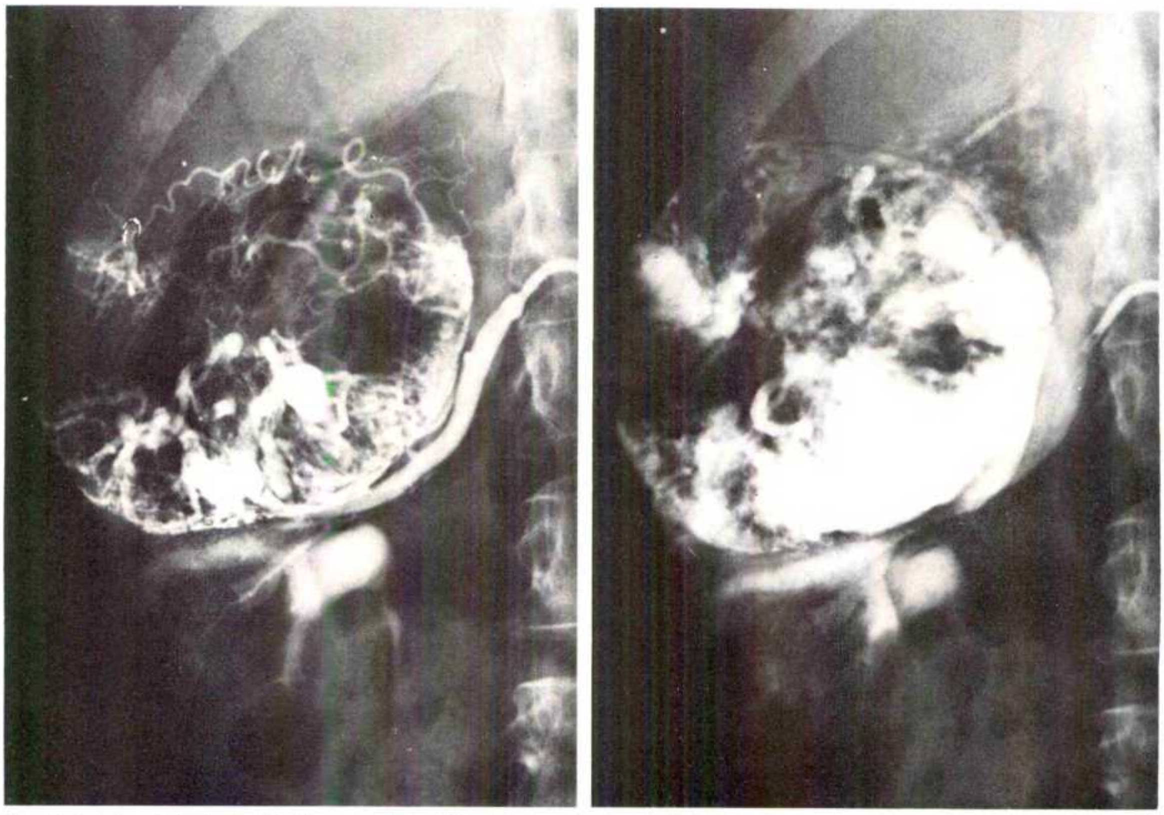

Fig. 3 (a) Arterial phase. (b) Venous phase. The right renal vein is normal. The adjacent inferior vena cava is also shown. There are small collateral veins.

correctly diagnosed in 20 of 21 examinations (95%) and the presence of tumour thombus was correctly diagnosed in 7 out of 8 examinations (87%). The overall accuracy was 96%.

Discussion

In a pathological study of 533 patients who underwent nephrectomy for renal carcinoma (Myers *et al.*, 1968), it was concluded that although the histological grade is the most important single factor determining prognosis in renal carcinoma, involvement of the renal vein is also a poor prognostic sign and is of particular significance in patients with low-grade tumours.

Macroscopic extension of renal carcinoma into the renal vein is seen in one-third to one-half of surgical specimens in renal adenocarcinoma (Evans and Bosniak, 1971).

While the renal veins are more likely to be involved if the tumour is centrally situated, tumours remote from the renal pelvis may produce tumour thrombus by propagation from the renal venous radicals.

Whilst histological invasion of the renal vein cannot be shown radiologically, the presence of tumour thrombus in the renal vein is usually associated with such invasion.

The conventional approach for renal exploration is an oblique lumbar incision. However, transabdominal nephrectomy is frequently employed for the removal of renal tumours. This approach permits a full exposure of the renal vessels which must be tied before the tumour is handled in order to prevent cells being dispersed into the circulation (Philip, 1971).

If the renal vein is shown to be involved by pre-operative radiological studies, many surgeons believe that the transabdominal approach is preferable to the oblique lumbar route in order that the renal vein can easily be clamped before handling the tumour.

For these reasons, and because selective renal phlebography may cause tumour spread, we evaluated large volume selective renal arteriography with follow-through as an alternative and safer way of showing the renal vein. While

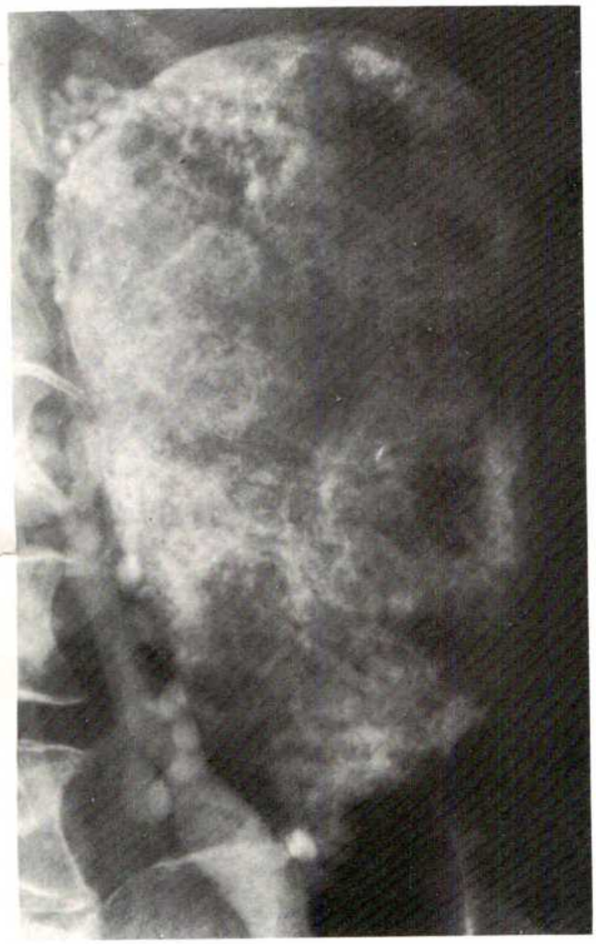

Fig. 4 Venous phase. The tumour is very large and the left renal vein is occluded. The ovarian vein is considerably dilated and functioning as a collateral vein.

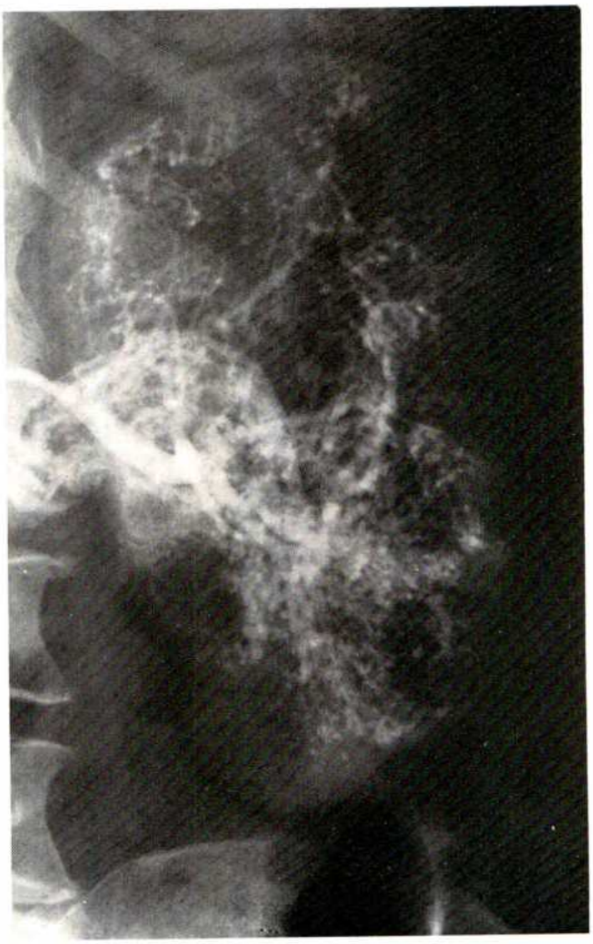

Fig. 5 Arterial phase (same patient as Fig. 4). The occluded left renal vein is shown by the striated pathological circulation in tumour thrombus.

we were collecting our data, Henriksson and Mikaelsson (1973) described a similar technique.

We chose the contrast medium meglumine iothalamate 60% because of its lower viscosity which allows easy hand injections.

Fifty millilitres of meglumine iothalamate 60% is a modest volume of contrast for an adult patient. Fifty millilitres injected selectively into a normal kidney, however, would be likely to cause renal damage. This consideration can be ignored in patients with renal carcinoma because the organ is to be removed.

In order to show the arterial phase and any pathological circulation a rapid series of exposures was made at the start of the injection, continuing with a slower run to ensure adequate coverage of the venous phase.

The fact that the renal veins tend to show more clearly in renal tumours is presumably related to the degree of vascularity and arteriovenous shunting which occurs in malignant tumours. The degree of vascularity of a tumour presumably accounts for the variation in the clarity with which the renal vein is shown; also, in very large tumours, 50 ml of contrast medium may be insufficient because of retention of contrast in the tumour circulation and larger volumes may be needed.

On the right side the renal vein lies in front of, and close to, the right kidney and may be overlapped by the contrast-filled renal pelvis. As the right renal vein is duplicated in about 25% of patients (Anson and Cauldwell, 1947) the demonstration of a single vein on this side does not exclude the possibility of a second vein being occluded by tumour. We did not encounter this situation ourselves, however. As duplication of the left renal vein occurs only in 1% of patients this problem rarely arises on this side.

The medial part of the left renal vein crosses the spine and is less easy to demonstrate in this part of its course because of the bone shadow.

An oblique projection, with the patient turned towards the side of tumour, reduces this overlapping and improves visualisation of the distal part of the renal vein. Tumour thrombus is unlikely to be found in the proximal part of the renal veins alone because the tumour thrombus spreads proximally along the renal veins.

Many of the problems of overlapping shadows due to soft tissues or bones causing inadequate visualisation of the renal veins can be overcome by the use of the subtraction technique (Fig. 1).

It has been suggested that the angiographic demonstration of collateral veins draining a renal carcinoma indicates, or strongly suggests, involvement of the main renal vein (Ahlberg *et al.*, 1966; Myers *et al.*, 1967; Genereux, 1968; Eisenman *et al.*, 1969).

However, other authors (Brindle, 1972; Whiteley *et al.*, 1974) have emphasised the fallibility of this sign and confirmed the desirability of diagnostic demonstration of the renal vein itself.

Henriksson and Mikaelsson (1973) found that thrombosis in the renal vein was not especially associated with the presence of collaterals. In our series those examinations with renal vein involvement did have collateral veins (Fig. 2) but these were also present in 4 patients with patent renal veins (Fig. 3). Thus the presence of collateral veins, such as the capsular, gonadal or lumbar veins, is an unreliable sign of main renal vein obstruction, although these may be more easily seen because of the vascularity of renal carcinomas. However, if the collateral veins are very large, this is considered a sign suggestive of main renal vein obstruction (Fig. 4).

In the one patient in whom we wrongly diagnosed renal vein thrombosis, no collaterals were demonstrated. With hindsight this should have alerted us to the possibility that the renal vein was not demonstrated for technical reasons.

Another angiographic sign of malignant renal venous thrombosis is a linear striated pattern in the arterial phase of the examination corresponding to the position of the renal vein (Kahn, 1965; Ferris *et al.*, 1968). This is thought to be due to the arterial supply to the intravenous component of the neoplasm (Gregg *et al.*, 1975). We observed this sign in 2 patients (Fig. 5).

In this small series of patients we have found large volume arteriophlebography both a safe and a reliable method of demonstrating or excluding tumour thrombus in the main renal veins, and the information obtained has proved useful to our surgical colleagues. We therefore suggest that this technique should form part of the routine assessment of patients with malignant tumours of the kidney.

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Single Sample Estimates of Renal Clearances

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Summary—Thirty adult patients were investigated with 36 ^{125}I Hippuran and 40 ^{51}Cr EDTA single injection clearance studies. "Volumes of distribution" obtained from single samples have been correlated with the slope clearances and regression equations have been determined. From these equations it is possible to determine glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) from single plasma samples and the method is sufficiently accurate for routine application.

Measurement of glomerular filtration rate (GFR) is widely considered to be essential in the clinical management of patients presenting with a wide range of nephrourological problems. The measurement of effective renal plasma flow (ERPF) is also frequently of clinical interest.

The standard methods for measuring GFR and ERPF using constant infusions of inulin and PAH respectively are, for all practical purposes, unsuitable in routine clinical practice.

Despite the large literature dealing with exogenous radionuclide clearance methods, the only technique to have achieved widespread routine clinical application is the endogenous 24-h creatinine clearance. This is not surprising as the only requirements from the patient are a single blood sample taken at any time and a 24-h urine collection, both of which can be dealt with easily by ward staff. For the adult patient confined to hospital, the creatinine clearance can normally provide a reliable measure of renal function. However, the problems associated with urine collection often result in inaccuracies which make the creatinine clearance method unsuitable, particularly for out-patients and children.

Radionuclide methods have been shown to give reliable results by many workers and have contributed to the reduction or elimination of some of the major problems associated with the more traditional methods. These problems arise essentially from (a) precision of dose injection, (b) urine collection inaccuracies, (c) inconvenience of constant infusion, (d) frequency of blood sampling, and (e) difficulties of chemical determinations. The problems associated with dose injection are common to all exogenous methods and can only be reduced with skill and practice. Single injection radionuclide clearance estimations can eliminate the problems arising from b, c and e. The frequent blood sampling normally associated with this method constitutes a major drawback and the accurate timing required aggravates the situation still further. The method has therefore remained somewhat unacceptable for routine use because, with all its simplicity, it remains complicated at the bedside.

It has been shown in recent years (Tauxe *et al.*, 1971) that accurate ERPF measurements can be made using a single blood sample. The technique has also been used for the measurement of GFR (Fisher and Veall, 1975) and for the simultaneous measurement of ERPF and GFR (Morgan *et al.*, 1977). The method relies on the experimental determination of an equation of regression between the multiple sample clearance and a "volume of distribution" calculated from the activity of a single blood sample.

The present study aimed to evaluate the reliability of this single injection, single blood sample, urineless radionuclide clearance method for both ERPF and GFR over a wide range of renal function.

Materials and Methods

A dose containing a known weight of 20 μc of ^{51}Cr-ethylenediamine tetraacetic acid (EDTA) and

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25 μc of ^{125}I orthoiodohippurate (Hippuran) was prepared and the activity of the syringe (including needle and cap) was counted in 2 channels of a scintillation counter before and after intravenous injection. This technique allowed an accurate calculation of the injected dose to be made. Prior to the injection a background blood sample was taken from the patient and, following injection of the dose, samples were taken at 10 min, 20 min, 44 min, 1 h, 3 h, 5 h, and sometimes 6 h.

All blood samples were spun and the supernatant plasma activity was measured using an automatic multichannel gamma sample changer. Background and separate diluted standards were also counted. Overlap corrections were made in the usual way and from the resulting data the ERPF and GFR were estimated from the Hippuran and EDTA clearances which were themselves derived from the equation:

$$\text{Slope clearance} = \text{zero time distribution volume} \times \text{plasma clearance constant}$$

The two-compartment model of Sapirstein *et al.* (1955) was used as the basis for the Hippuran clearance, using the 44 to 60 min data for obtaining the residual slope. A single-compartment analysis was used for the GFR from the 3 to 5 h data together with a suitable correction factor in a manner similar to that used by Chantler *et al.* (1969).

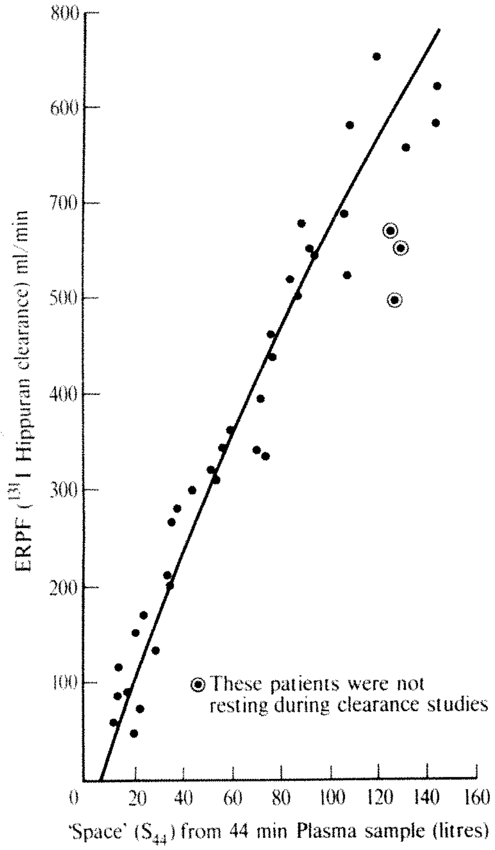

Fig. 1 The ERPF (Hippuran slope clearance method) plotted against the "space" obtained from the 44-min plasma sample (S_{44}). The equation which best fits the data (excluding the non-resting patients) is: $ERPF = 120\,(S_{44} + 56)^{1/2} - 936$ and the standard deviation of the clearance data from this line is 46 ml/min.

Patients were normally resting in bed during the test but in some cases the staff volunteers carried on their normal activities throughout the 5-h period. Oedematous patients were not selected as their equilibration time is protracted (Chantler *et al.*, 1969).

A Hippuran "volume of distribution" (space) was calculated from the 44-min plasma activity using the equation:

$$S_t = \text{Dose}/P_t$$

where S_t is the "space" at time "t" and P_t is the plasma activity at time "t".

Similarly, an EDTA "space" was calculated from each of the 2, 3, 4 and 5-h plasma activities. The 2-h and 4-h values were interpolated from the plasma activity-time curve.

Thirty non-oedematous adult patients were investigated with 38 ^{125}I Hippuran and 40 ^{51}Cr EDTA single injection clearance studies (36 were simultaneous).

Results

The "spaces" obtained from the equation above bear a good correlation with the clearance estimates as shown in Figures 1 and 2. The time chosen for the Hippuran "space" (Fig. 1) was 44 min following the work of Tauxe *et al.* (1971), who demonstrated that the standard deviation from their regression was at a minimum at this time. In the case of the EDTA "space" the 2, 3, 4 and 5-h plasma activities were used to calculate 4 separate "spaces" in a manner similar to that used by Fisher and Veall (1975). Good correlation was found between the "spaces" and clearances at each of the sampling times, but the best correlation over the widest range of clearances was that obtained with the 3-h space and this is shown in Figure 2. There was no improvement in the

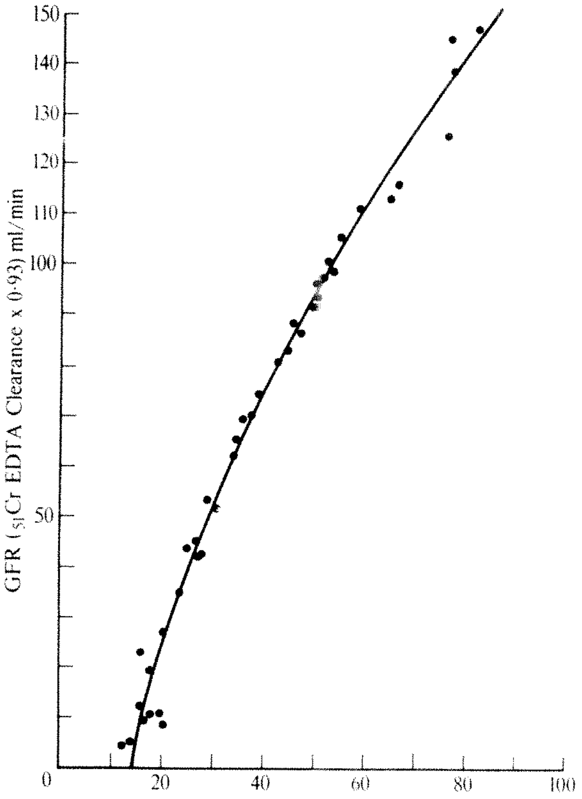

Fig. 2 The GFR (EDTA slope clearance method) plotted against the "space" obtained from the 3-h plasma sample (S_3). The equation which best fits the data ia: $GFR = 24.5\ (S_3 - 6.2)^{1/2} - 67$ and the standard deviation of the clearance data from this line is 4.4 ml/min.

correlation when clearances were corrected for body surface and spaces corrected for body weight.

The equations best fitting our data were found to be:

$$GRF = 24.5\ (S_3 - 6.2)^{1/2} - 67$$
$$\text{and } ERPF = 120\ (S_{44} + 56)^{1/2} - 936$$

where S_3 and S_{44} are the "space" values determined for EDTA and Hippuran at 3 h and 44 min respectively.

Over the complete range the standard deviation is 4.4 ml/min from the GFR curve and 46 ml/min from the ERPF curve.

Discussion

It has been shown that, in accordance with the findings of previous workers, the "space" determined from a single plasma sample can be used to determine a reliable estimate of the EDTA clearance. This finding also applies, though with less accuracy, to the determination of the Hippuran clearance. Furthermore, both clearances can be obtained simultaneously from the 2 "spaces" calculated from the activities of 2 plasma samples taken at 44 min and 3 h following a single injection with a double isotope.

The GFR estimates obtained in this way are inaccurate at low values but more reliable than the ERPF estimates, as can be seen from the better correlation. However, the ERPF data, which fall well away from the best-fit line, do so in some cases as a result of a known factor rather than from random error. As indicated in Figure 1, 3 of those points lying below the line were obtained from "normal subjects" who were not resting during one investigation and only their resting values were used in obtaining the regression equation. No similar departures were observed in the GFR data. These differences between resting and non-resting patients are in agreement with the known physiological effects of exercise (Pitts, 1968).

It can be concluded that a reliable estimate of the GFR can be obtained in non-oedematous patients from a single 3-h plasma sample and that this reliability is maintained even when the patient does not observe an exacting regime of rest during the 3-h period between the dose and the blood sample. The technique is therefore well suited to attendances at the out-patients' clinic; it eliminates or significantly reduces most of the problems arising from the more traditional methods and is left with the unavoidable difficulties associated with a good intravenous injection. It has also been shown that less reliable simultaneous estimates of ERPF may also be obtained. For this measurement, our results suggest that patients should be resting and in practice this would mean until the 44 min blood sample had been taken.

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Familial Renal Hypouricaemia: Two Additional Cases with Uric Acid Lithiasis

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Summary—Two families are reported affected with hereditary renal hypouricaemia associated with uric acid lithiasis. The propositi of both families were found also to have hyperabsorptive hypercalciuria.

Based on the study of the effect of pyrazinamide and probenecid on uric acid excretion in both propositi, it is suggested that the defect in uric acid reabsorption is most probably at the pre-secretory site.

Hypouricaemia resulting from a genetically determined defect in the renal handling of urate is rare, appearing usually as one of the many manifestations of the multiple defects in tubular function associated with disorders such as the Fanconi syndrome (Wallis and Engle, 1957) or Wilson's disease (Bishop *et al.*, 1954). However, cases have been reported in which genetic renal hypouricaemia has not been associated with such broad tubulopathies but has occurred either as an isolated defect (Praetorius and Kirk, 1950; Khachadurian and Arslanian, 1973; Benjamin *et al.*, 1977; Sperling *et al.*, 1977), or else in association with hypercalciuria (Greene *et al.*, 1972; Sperling *et al.*, 1974). During the past 5 years we have reported on 3 families with these isolated types of genetic renal hypouricaemia; in one of these families the renal hypouricaemia was associated with hypercalciuria and decreased bone density (Sperling *et al.*, 1974), whilst in the other 2 it appeared as an isolated defect (Benjamin *et al.*, 1977; Sperling *et al.*, 1977).

In this paper we describe 2 additional unrelated families with renal hypouricaemia. In the propositi of these families the renal hypouricaemia was associated with hyperabsorptive hypercalciuria and uric acid lithiasis.

Patients and Methods

M.E., a 37-year-old Israeli-born Jew of Iraqi origin, developed recurrent renal colic associated with fever, chills and vomiting in 1968. In 1972 X-rays revealed a partially calcified stone in the right kidney. In October 1973 he underwent operation for the removal of several stones composed mainly of uric acid, though some also contained calcium oxalate. In August and October 1976 the patient suffered several attacks of left renal colic and voided stones of the same composition. On the present admission the patient was asymptomatic. His body weight was 76 kg and his height 175 cm. Physical examination and routine haematological and blood chemistry values were all within the normal range, except for a low serum uric acid level (see Results). Serum ceruloplasmin and copper levels were within the normal range. There was no glycosuria or phosphaturia and the urinary pattern of amino acids was normal. Creatinine clearance ranged from 93 to 121 ml/min and morning urinary pH was 5.0 to 6.0. A bone survey showed no abnormality.

Patient M.S., a 39-year-old Bulgarian-born Jew of Turkish origin, first developed recurrent bilateral renal colic in 1961. In 1964 he passed 2 stones composed of uric acid and calcium oxalate. In 1975 he developed fever, chills, dysuria and haematuria. X-rays showed a staghorn stone in the left kidney and a small stone in the right kidney. In January 1976, because of hydronephrosis, the staghorn stone was removed. The nucleus of the stone was found to be composed of uric acid, and the remainder of uric acid, calcium oxalate and phosphate. Following forced diuresis for 2 months, the stone from the right kidney was spontaneously voided. This stone was composed of uric acid and calcium oxalate. On admission his body weight was 84 kg and height 174 cm. All routine tests as well as physical examination did not reveal any abnormality except for hypouricaemia and hypercalciuria (see Results). There was no glycosuria, phosphaturia or aminoaciduria. Serum ceruloplasmin and copper levels were normal. Morning urinary pH was 5.0 to 7.0. A bone survey showed no abnormality.

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For the study of renal urate handling the 2 patients were maintained on regular hospital diets. Uric acid was determined by an enzymatic spectrophotometric method (Liddle *et al.*, 1959). Pyrazinamide (PZA) suppression tests and probenecid tests were performed by the technique of Benjamin *et al.* (1977). For the study of urinary calcium excretion the patients were put on a low calcium diet containing 400 to 500 mg calcium per day. Urinary calcium was measured by Technicon Auto Analyser II Methodology.

Results

Effect of Pyrazinamide (PZA) and Probenecid on Renal Urate Excretion

In the patients M.E. and M.S., serum urate level ranged from 1.0 to 1.1 mg% and from 1.0 to 1.2 mg% respectively. Urate clearance, as measured in 20 min periods, averaged 60 ml/min in patient M.E. and 80 ml/min in M.S. In both patients administration of PZA caused only a small decrease in urate clearance, the fractional excretion of uric acid (Clearance of urate/Clearance of creatinine × 100) decreasing in M.E. from 45 to 28.2% and in M.S. from 48 to 16.8% (Table 1). Probenecid administration did not cause a significant change in uric acid excretion in either patient (Table 2).

Calcium Excretion

When on a regular home diet, patient M.E. excreted up to 390 mg calcium/24 h and patient M.S. up to 528 mg/24 h. After the patients had been on a low calcium diet (400-500 mg calcium/day) for one week, the urinary calcium fell to 120 mg/day in patient M.E. and 210 mg/day in M.S.

Table 1 Effect of Pyrazinamide Administration on Uric Acid Excretion

*Period**	$\frac{\text{Clearance of urate}}{\text{Clearance of creatinine}}$ × *100 in patient*	
	M.E.	*M.S.*
Control	45.0	47.9
PZA, 3.0 g orally		
1	43.4	44.0
2	35.7	35.1
3	38.4	32.9
4	33.9	22.7
5	29.0	20.8
6	28.2	16.8
7	-	31.4

* Each period is of 20 min.

Table 2 Effect of Probenecid Administration on Uric Acid Excretion

*Period**	$\frac{\text{Clearance of urate}}{\text{Clearance of creatinine}}$ × *100 in patient*	
	M.E.	*M.S.*
Control	58.2	55.0
Probenecid, 2.0 g orally		
1	59.4	60.6
2	71.6	60.0
3	72.5	-
4	67.5	47.0
5	70.0	44.3
6	65.7	48.7
7	67.0	43.7

* Each period is of 20 min.

Study of the Families

Both propositi are the offspring of non-consanguineous marriages (Fig.). Blood samples were obtained from all available relatives (Tables 3 and 4). Two of M.E.'s sisters and one of M.S.'s brothers were found to have frank hypouricaemia. Rather low serum urate levels were found in other members of both families.

Discussion

Both patients were found to be affected with renal hypouricaemia which was associated with hypercalciuria but with no other renal tubular or metabolic abnormality. When the patients were put on a low calcium diet their urinary calcium excretion fell into the normal range, a finding which suggests that both were affected with the hyperabsorptive rather than the renal type of hypercalciuria. The renal hypouricaemia in the 2 propositi would appear to be familial since each of them was found to have siblings with abnor-

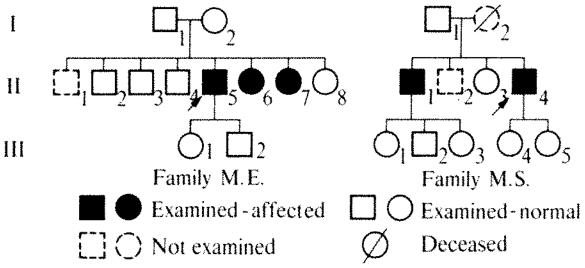

Fig.

Table 3 Serum Uric Acid Levels in Members of Family M.E.

Subject		*Age*	*Serum urate (mg%)*
Propositus	II—5	37	1.3-2.1
Father	I—1	75	3.3
Mother	I—2	60	3.7
Brothers	II—2	29	4.0
	II—3	36	5.2
	II—4	41	4.1
Sisters	II—6	24	1.3
	II—7	27	2.2
	II—8	47	3.9
Children	III—1	12	3.6
	III—2	8	4.0

mally low serum urate levels. The data obtained from the studies of the 2 families do not permit an accurate assessment of the pattern of inheritance, but the disorder was not found in any children of affected individuals, both sexes were affected and, especially in the family of M.E., several individuals were found to have serum urate levels which may indicate heterozygosity. These findings suggest that the renal hypouricaemia is inherited as an autosomal recessive defect. Unfortunately it was not possible to determine whether the hypercalciuria found in the propositi was also familial or merely fortuitous because no urine samples were obtained from their relatives. In the familial syndrome of hypouricaemia, hypercalciuria and decreased bone density reported by Sperling *et al.* (1974) the hypercalciuria was shown to be genetic and inseparable from the hypouricaemia, but it cannot be assumed that a similar relationship would have been observed in the families reported here because no skeletal abnormality was found in either propositus. However, it may be significant that Greene *et al.* (1972) have reported the association of hyperabsorptive hypercalciuria and familial hypouricaemia in a case of renal lithiasis.

Table 4 Serum Uric Acid Levels in Members of Family M.S.

Subject		*Age*	*Serum urate (mg%)*
Propositus	II—4	39	1.0-1.7
Father	I—1	72	4.7
Brother	II—1	42	2.2
Sister	II—3	35	2.5
Children	III—4	21	4.4
	III—5	24	3.6
Brother's children			
	III—2	19	5.5
	III—3	17	5.2

The pathogenesis of renal hypouricaemia is still uncertain but there is evidence to suggest that it may result from several defects of tubular function. Rieselbach and Steele (1974) have proposed that the renal handling of urate in man normally comprises 4 processes: glomerular filtration, proximal reabsorption, secretion and post-secretory reabsorption. Furthermore, they suggest that virtually all the filtered urate is reabsorbed by the proximal, or pre-secretory mechanism, and that the rate of urate excretion is regulated mainly by changes in post-secretory reabsorption. Assuming that this model is correct, an abnormally high urate clearance could be due, in theory, to defective reabsorption at either the pre-secretory or the post-secretory site or at both sites. The results of the PZA suppression test in cases of renal hypouricaemia suggest that all 3 varieties of the condition do in fact occur (Rieselbach and Steele, 1974). In healthy subjects PZA, which inhibits tubular secretion of urate, causes an almost complete suppression of uric acid excretion (Steele and Rieselbach, 1967). A similar effect has been reported in some cases of renal hypouricaemia (Bennett *et al.*, 1972; Wilson and Goldstein, 1973). In these cases it would appear that a defect in post-secretory reabsorption is responsible for the high urate clearance. In contrast, the high urate clearance in the cases described by Greene *et al.* (1972) and Sperling *et al.* (1974) is probably due to a defect in pre-secretory reabsorption since it fell but still remained abnormally high following the administration of PZA. In a third group of cases the high urate clearance would appear to result from a total loss of tubular reabsorption because it exceeded creatinine clearance and, in the one instance when it was given, PZA reduced the urate:creatinine clearance ratio to approximately 1 (Praetorius and Kirk, 1950; Khachadurian and Arslanian, 1973; Simkin *et al.*, 1974).

In the 2 patients described here the urate:creatinine clearance ratios were less than 1 and PZA had a minimal effect on urate excretion. Accordingly it is suggested that both have a defect in pre-secretory reabsorption. This assumption is supported by the insensitivity of their urate excretion to probenecid, which normally increases urate clearance manyfold (Sirota *et al.*, 1952; Gutman and Yu, 1957).

The association of bilateral recurrent uric acid lithiasis with renal hypouricaemia in these 2 patients is probably not fortuitous. It is well recognised that urate is not excreted solely by the kidney; some is secreted into the intestine where it undergoes bacterial degradation (Wyngaarden, 1972). In renal hypouricaemia an abormally small amount of urate will be secreted into the gut and hence a greater proportion of the total urate produced will be excreted in the urine. In both our patients uric acid excretion frequently exceeded 1000 mg/24 h when they were on their regular home diets. This hyperuricosuria, when associated with low urine output and pH, common findings in the Israeli hot summer climate, is likely to predispose to stone formation (Atsmon *et al.*, 1963). The composition of the calculi in these patients suggests that their diet-dependent hypercalciuria also may have contributed to the formation of their stones. At present both patients are being treated with Allopurinol, a low calcium diet and a forced fluid intake. Repeated examination of morning urines has not revealed any crystals but a long period of follow-up will be needed to evaluate the efficacy of this treatment.

As a final point of interest, 5 of the few reported families with the isolated type of renal hypouricaemia are Israeli Jews of non-Ashkenazi origin. This suggests that there may be a relatively high incidence of this rare disorder among non-Ashkenazi Jews.

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False-negative Saralasin Responses in Renovascular Hypertension

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Summary—Blood pressure responses to the infusion of saralasin and plasma renin levels were measured in 31 hypertensive patients following preparation with frusemide. Five patients had unilateral renal artery stenosis, with renal vein renin ratios lateralising strongly to the affected side. Saralasin produced depressor reponses in 3 of these but failed to evoke significant effects in the other 2, despite the fact that in both cases hypertension was subsequently alleviated by renal bypass surgery. A further period of more severe sodium depletion increased plasma renin levels and the depressor effect of saralasin, but did not help to differentiate renal artery stenosis from other forms of hypertension.

Because it is generally agreed that the renin-angiotensin system has a primary role in the pathogenesis of renovascular hypertension, much attention has been given to renin tests as a means of diagnosing this condition. Measurement of peripheral plasma renin activity has thus been advocated as a good way of screening for renal artery stenosis in hypertensive populations (Swales, 1976), while bilateral renal vein renin sampling has been shown repeatedly to have prognostic value in predicting which patients will benefit from surgical correction of renal artery stenosis (Stockigt *et al.*, 1972; Hussain *et al.*, 1973; Melman *et al.*, 1977). More recently, interest has focused on the use of angiotensin blockade by saralasin (1-sar-8-ala-angiotensin II) as a means of detecting renovascular hypertension and it has been suggested that this approach yields fewer false-negative results than when reliance is placed upon peripheral or renal vein renin determinations (Streeten *et al.*, 1975; Marks *et al.*, 1976 and 1977).

Against the background of our experience with a standard saralasin infusion test (Streeten *et al.*, 1976) in hypertensive patients, we report false-negative saralasin responses in 2 patients with functional renal artery stenosis.

Patients and Methods

The subjects of this study were 31 hypertensive patients comprising 8 with renal artery stenosis (5 unilateral and 3 bilateral), 11 with renal parenchymal disease and 12 with essential hypertension (Table). The last 2 subgroupings were based on clinical examination, intravenous or retrograde pyelography and measurement of creatinine clearance, which were carried out in every case. Renal arteriography was carried out in 2 of the patients with essential hypertension and 3 with renal parenchymal disease, in addition to the cases in which renal artery stenosis was diagnosed. Renal vein renin concentrations were determined following diazoxide stimulation (Stokes *et al.*, 1976) in 6 patients. Each of the 5 patients with unilateral renal artery stenosis underwent renal artery bypass surgery after their investigations had been completed. Four showed sustained improvement in blood pressure but one case, with bilateral renal cortical scarring and caliceal clubbing due to analgesic nephropathy, failed to respond.

In all cases, antihypertensive therapy was withdrawn for one week or longer and then baseline plasma renin activity was determined as previously reported (Stokes *et al.*, 1976). The values obtained were graded as low, normal or high by reference to a nomogram relating 118 determinations of peripheral plasma renin activity (erect posture) to concurrent urinary sodium excretion in 76 normal volunteers. Frusemide-stimulated plasma renin activity and blood pressure responses to saralasin

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Table Summary of Findings in 31 Hypertensive Patients

Group	*Diagnosis*	*No.*	*Mean age*	*Mean serum creatinine concentration* mmol/l	*Mean sodium deficit mmol*		*Mean plasma renin activity pmol/l/s*		*Average response in mean BP (mmHG) to saralasin 10 μg/kg/min*	
					A	B	A	B	A	B
I	Essential hypertension	12	49	0.09	112	272	0.51	1.48	+4.3 (−8 to +16)*	−8.1 (−26 to +8)
II	Renal parenchymal disease	11	60	0.21	89	259	0.58	1.46	+1.5 (−5 to +14)	−12.2 (−22 to −3)
III	Unilateral renal artery stenosis	5	35	0.09	122	204	2.16	3.60	−11.6 (−26 to −3)	−25.8 (−36 to −18)
IV	Bilateral renal artery stenosis	3	59	0.18	95	351	0.60	n.a.	+1	−23

* Values in parentheses denote the range of responses.

A = Values obtained 3 to 4 h after intravenous injection of frusemide 40 mg.

B = Values obtained after a 48-h period of further sodium depletion in 19 patients (8, 5, 5 and 1 of the patients in Groups I to IV respectively).

n.a. = Not available.

infusion were determined using a standard protocol (Streeten *et al.*, 1976) according to which saralasin 0.1 to 10 μg/kg/min is infused 3 h after an intravenous injection of frusemide 40 mg. A second saralasin test was performed in 19 of the patients after they had been subjected to further sodium depletion over a 48 h period by a 10 mmol sodium diet and administration of frusemide 160 mg (in divided oral doses). Change in blood pressure during saralasin testing was expressed as the difference between the mean control reading and the average of 3 consecutive readings taken during the peak response to the highest rate of analogue infusion (10 μg/kg/min). In normal subjects, the maximum falls in systolic and diastolic pressure observed by other workers using this test were 10 mmHg and 7 mmHg respectively (Streeten *et al.*, 1975). Almost all patients with greater depressor effects were shown to have evidence of renal ischaemia (Streeten *et al.*, 1975 and 1976).

Results

The case histories of 4 patients are given in detail, to illustrate the difficulty in distinguishing essential from renovascular hypertension on the basis of saralasin responses.

Case 1 Essential hypertension, normal peripheral renin levels

A 41-year-old woman was referred for evaluation of severe hypertension. Intravenous pyelography showed that the left kidney was 2.0 cm greater in length than the right, but that the caliceal patterns were normal and there was no delay in contrast excretion. A micturating cystourethrogram revealed no ureteric reflux. No renal or renovascular lesions were demonstrable by arteriography (Fig. 1). Peripheral plasma renin activity was well within normal limits and renal vein renin determinations were not performed. At the highest rate of saralasin infusion (10 μg/kg/min) there was a small depressor effect of borderline significance, averaging 11 mmHg systolic pressure and 7 mmHg diastolic (Fig. 1).

Whereas most of the cases without renal artery stenosis had no appreciable response to saralasin, or mild rises in blood pressure, this patient's response was depressor. However, plasma renin activity was normal and there was no arteriographic evidence of renal ischaemia. Renal function was normal. A diagnosis of essential hypertension was made.

Case 2 Hypertension, left renal artery stenosis, elevated peripheral renin levels

A 30-year-old woman was referred with a 3-month history of hypertension. Intravenous pyelography showed that both kidneys were of normal contour, but the left was 3.3 cm less in length than the right and showed delayed caliceal filling. Aortography revealed severe stenosis of the left renal artery with aneurysmal post-stenotic dilatation; unstimulated peripheral plasma renin activity was very high and the diazoxide-stimulated

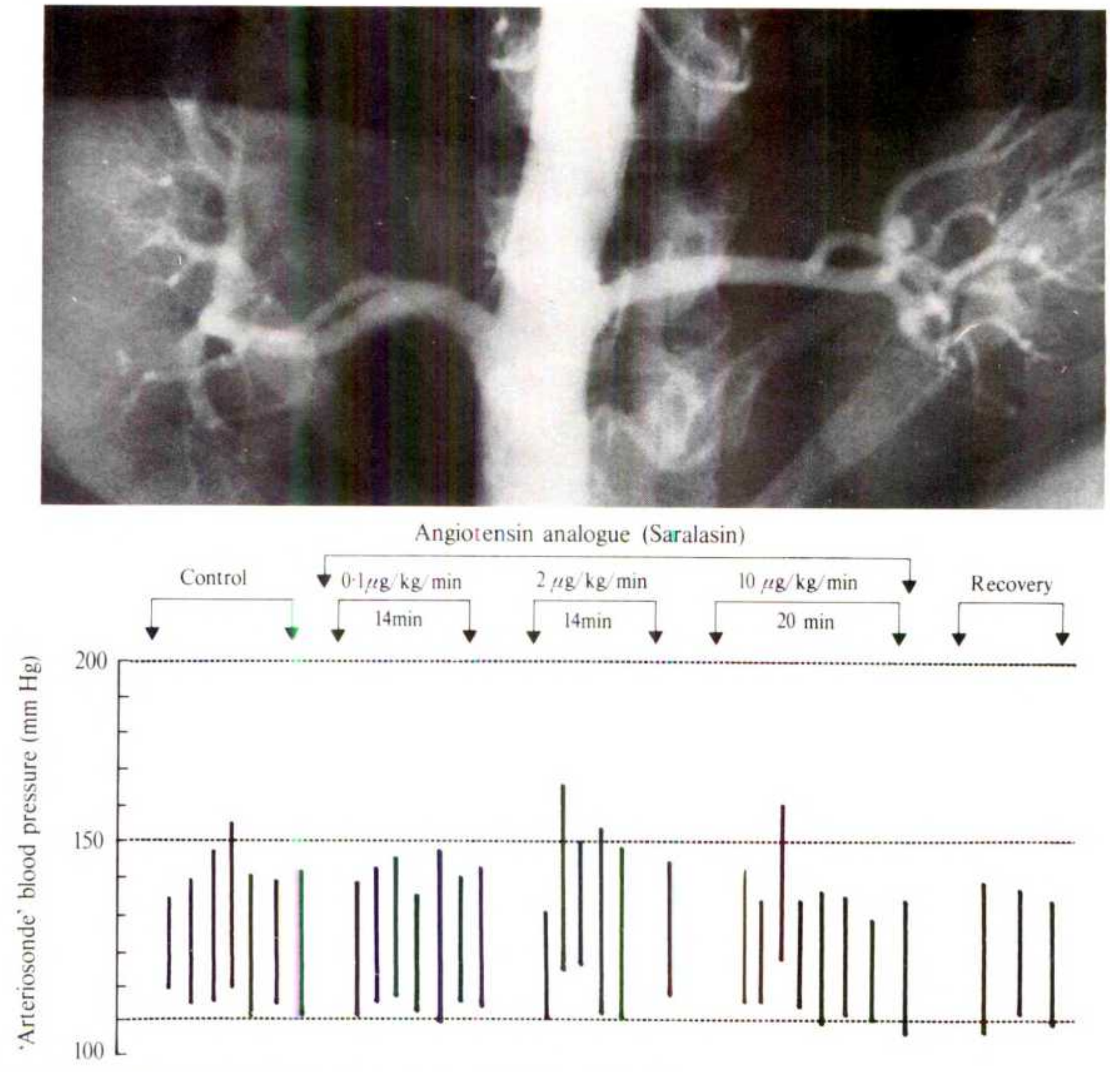


Fig. 1 *Case 1.* (HF) Essential hypertension, normal peripheral renin levels.

renal vein renin ratio lateralised to the left (Fig. 2). At the highest rate of saralasin infusion there was a pronounced depressor effect averaging 15 mmHg systolic pressure and 14 mmHg diastolic. Following splenorenal arterial anastomosis blood pressure fell to normal. Post-operative arteriography showed that the bypass functioned well and 3 months after operation the blood pressure was 120/80 without therapy.

The saralasin response here was consistent with the hyperreninaemia, renal vein renin lateralisation, radiological findings and operative result. This was not so in the next 2 cases, in which reliance upon saralasin testing alone could have excluded the opportunity for surgical cure.

Case 3 Hypertension, right renal artery stenosis, elevated peripheral renin levels

A 23-year-old woman with hypertension was found to have a systolic bruit in the epigastrium and pyelography revealed that the right kidney was smaller than the left. She was referred for renal arteriography, which showed a segment of fibromuscular hyperplasia, with stenosis, in the right renal artery. Peripheral plasma renin activity was greatly increased and the renal vein renin ratio indicated right renal ischaemia. However, standard saralasin tests failed on 2 separate occasions to evoke a clear-cut depressor response: although a small depressor effect was observed with 2 µg/kg/min, no appreciable response occurred with 10 µg/kg/min (Fig. 3). The right renal artery was repaired by excising

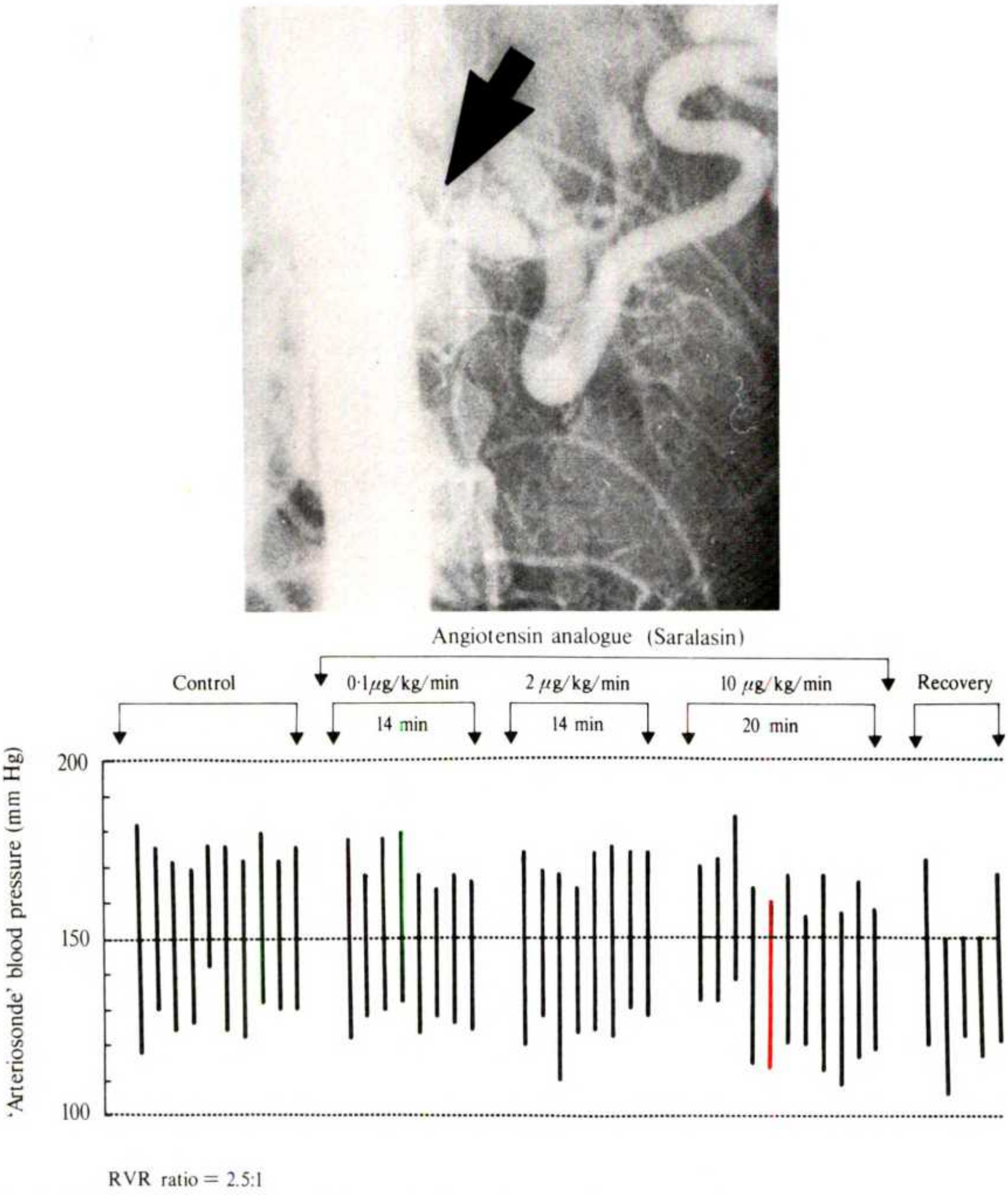


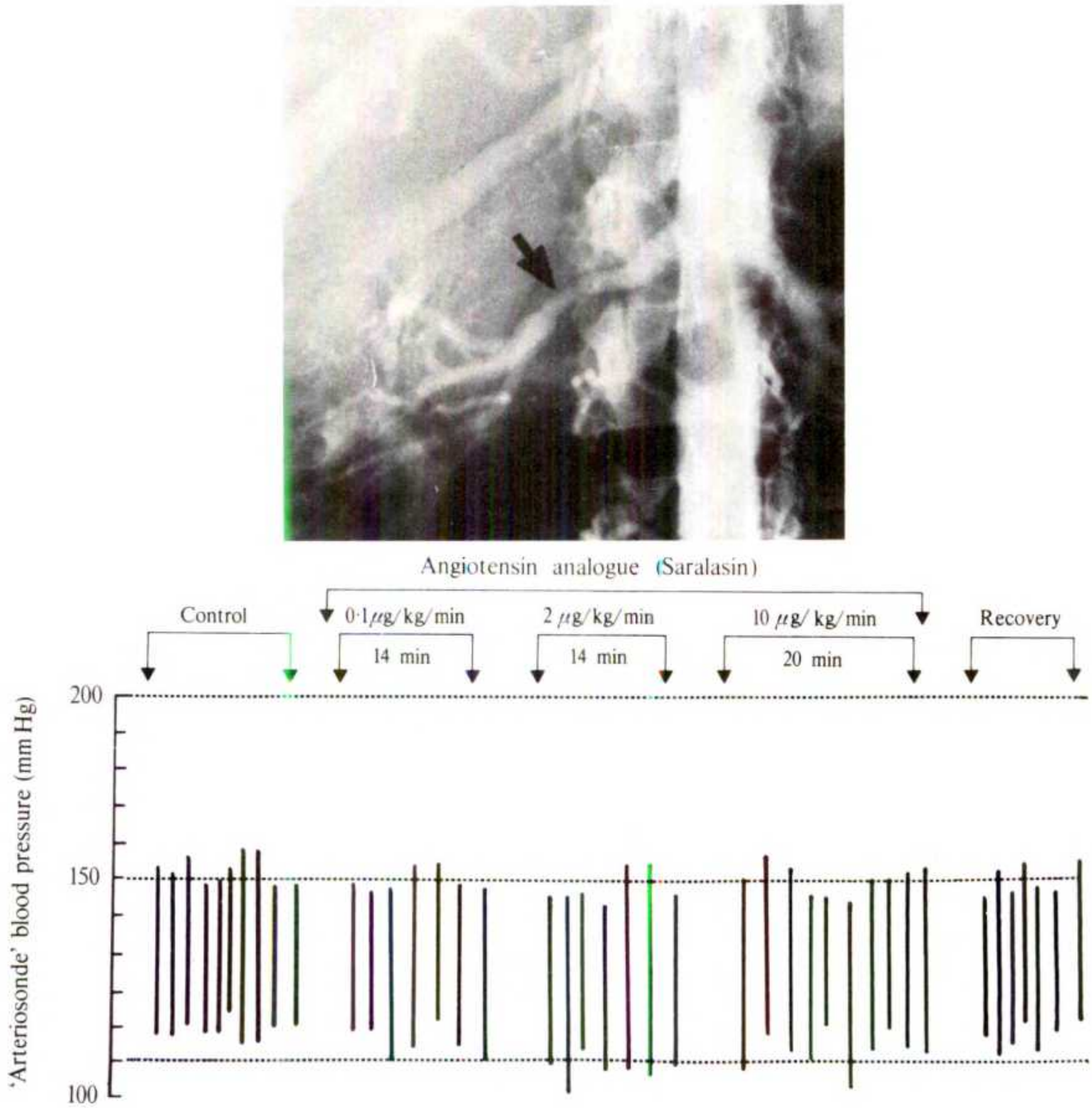
Fig. 2 *Case 2.* (JH) Hypertension, left renal artery stenosis, elevated peripheral renin levels.

the stenosed segment and interposing a saphenous vein graft. Four months after operation the blood pressure was normal (130/80) without treatment.

Despite the strong evidence for a diagnosis of angiotensinogenic hypertension, saralasin failed to evoke a definite depressor effect.

Case 4 Hypertension, right renal artery stenosis, normal peripheral renin levels

A 33-year-old woman was investigated for severe hypertension of recent origin. Upon auscultation of the abdomen a systolic bruit was heard just above the umbilicus. Selective arteriography revealed fibromuscular hyperplasia and tight stenosis of the right renal



RVR ratio = 2·6:1

Fig. 3 *Case 3.* (PT) Hypertension, right renal artery stenosis, elevated peripheral renin levels.

artery (Fig. 4) with minimal irregularity and no narrowing of the left. The diazoxide-stimulated renal vein renin ratio showed strong lateralisation to the right. However, unstimulated peripheral plasma renin activity was in the middle of the normal range and the initial saralasin infusion caused only a small fall in diastolic pressure without a drop in the systolic level (Fig. 4). One year after a successful saphenous vein bypass of the right renal artery stenosis, the patient's blood pressure was 132/86 on minimal therapy (propranolol 40 mg daily given to control atrial extrasystoles). By comparison, pre-operative blood pressure readings were 180/130 without treatment and 165/110 during treatment with propranolol 180 mg daily.

The clinical and radiological features of this patient, together with the diazoxide-stimulated renal vein renin levels, indicated that right renal ischaemia was the dominant cause of her hypertension. Yet peripheral renin activity was normal and the response to a standard saralasin test was only mildly depressor, being within the range observed in essential hypertension.

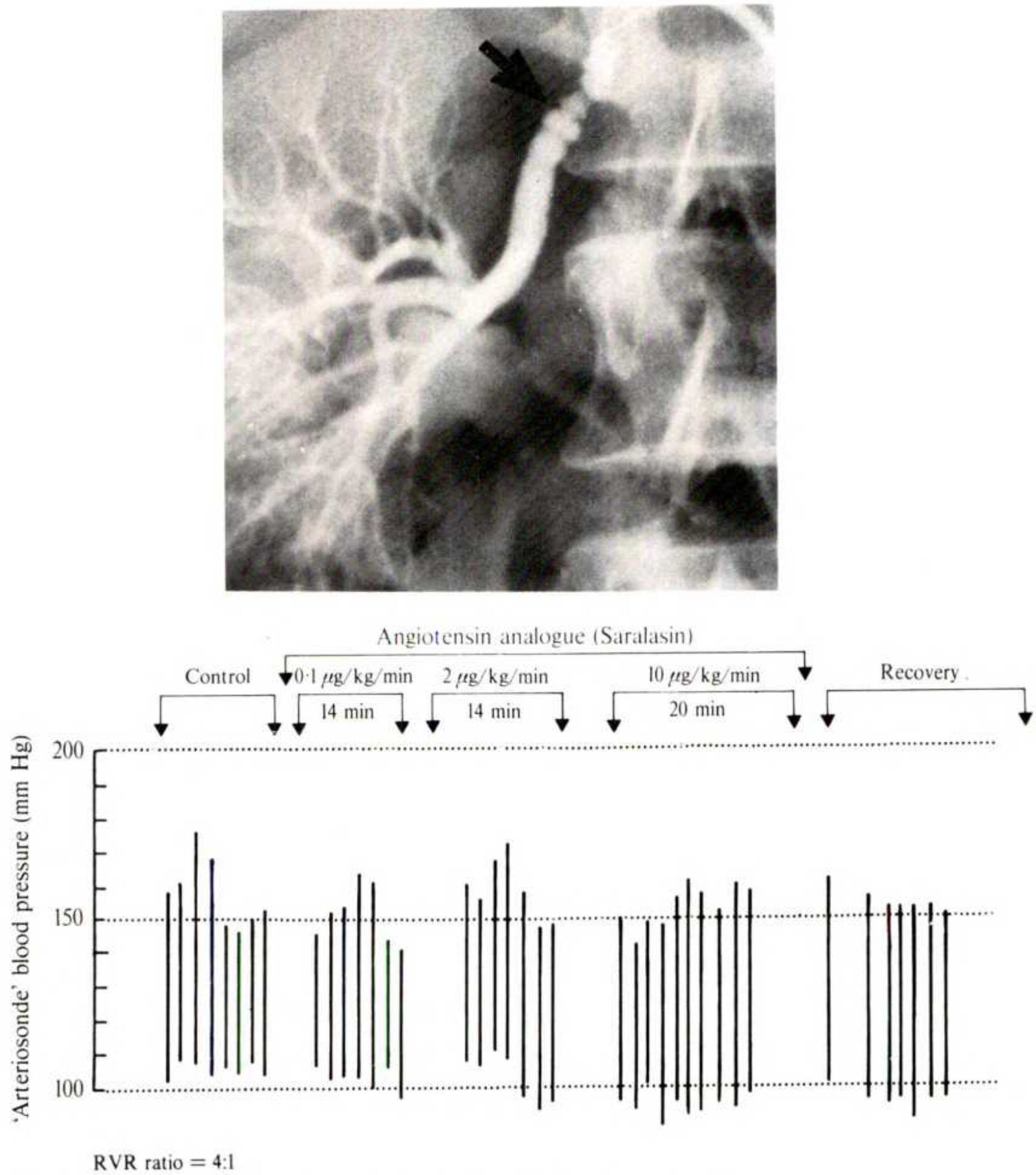


Fig. 4 *Case 4.* (JP) Hypertension, right renal artery stenosis, normal peripheral renin levels.

Overall Findings

In the other 2 cases of unilateral renal artery stenosis in this series, the renal vein renin ratios also showed lateralisation to the involved side (3.3:1 and 1.7:1 respectively). In one case of bilateral renal artery stenosis (not subjected to bypass surgery) the ratio lateralised to the more affected side (1.8:1). In the other 2 patients with bilateral stenosis, renal vein renins were not determined.

Data from the 4 diagnostic groups of patients are shown in the table, in which mean values for sodium deficit (derived from sodium balance data), plasma renin activity and blood pressure response to saralasin are given for both the standard test (A) and for the test conducted after more severe sodium depletion (B). Overall, there was a high degree of correlation between saralasin-induced change in mean blood pressure and plasma renin activity ($r=0.752$, $P<0.001$).

Results Obtained Following a Single Dose of Frusemide 40 mg iv

Although mean blood pressure (diastolic plus one-third of pulse pressure) decreased during saralasin infusion in all 5 patients with unilateral renal artery stenosis, the depressor effect was equivocal in one case (Case 3) and minimal in another (Case 4). The sodium deficits in Cases 3 and 4 were 129 and 238 mmol respectively, compared with 53, 50 and 129 mmol in the other 3 patients. One of the patients with essential hypertension (Case 1), 3 with renal parenchymal disease (including one in whom renal artery stenosis was excluded definitively by arteriography) and one with bilateral renal artery stenosis had responses which fell within the range for unilateral stenosis. The other 2 bilateral stenosis cases had mild pressor responses. Unstimulated plasma renin activity was above normal, as defined by the renin-sodium nomogram, in 4 of the 5 patients with unilateral stenosis, but was also raised in 3 other patients (2 with parenchymal disease, 1 with bilateral stenosis). Mean plasma renin activity after frusemide stimulation was higher in the unilateral stenosis group than in the others (Table) but, again, the ranges overlapped.

Results Obtained after Further Sodium Depletion

After dietary sodium deprivation and further diuretic therapy, pronounced depressor responses occurred during saralasin infusion in all 5 patients with unilateral renal artery stenosis. Among the other groups too, however, most responses to saralasin were now depressor and of the 14 patients tested, 4 (including the one with bilateral stenosis and a lateralising renal vein renin ratio) had responses within the range observed in those with unilateral stenosis. Values for plasma renin activity during sodium depletion were generally higher in the unilateral stenosis group than in the remainder.

Discussion

We believe that saralasin testing is of very limited value in determining whether hypertensive subjects have functional renal artery stenosis. This conclusion is based on our findings in the 2 patients with unilateral renal artery stenosis and lateralising renal vein renin ratios whose post-operative progress after renal bypass confirmed that they had had renal ischaemia. Before an arterial repair, one of these patients showed a minimal depressor response to saralasin given under standard conditions (Streeten *et al.*, 1976) and the other responded equivocally. From a clinical diagnostic viewpoint both responses must be regarded as false-negatives, for neither was classifiable as positive for angiotensinogenic hypertension. Indeed, they resembled the effects obtained in several of the other patients tested, including 2 in whom renal artery stenosis was excluded by arteriography.

After more severe sodium depletion, which increased plasma renin levels and the prevalence of responses to saralasin in every group, all 5 patients with unilateral renal artery stenosis had strongly "positive" responses. However, this was achieved at the expense of producing more "false-positives" among the other groups.

In considering the relative merits of diagnostic procedures used in detecting curable hypertension, it is important to distinguish between those which are useful in primary screening and those which are usually confined to cases in which a curable cause is strongly suspected. With the first type, which must be simple and economical to perform, the occurrence of false-positive results is acceptable provided that they can be recognised later by more specific tests. However, the incidence of false-negatives (which lead to curable cases being missed) should be very low. With the second type of test, expense is not as great a consideration, for fewer patients are involved, but diagnostic specificity becomes critical.

The major disadvantage with current screening procedures for renovascular hypertension is that they produce an appreciable incidence of false-negative results. This applies not only to auscultation for renal artery bruits, to rapid-sequence pyelography and to determination of peripheral plasma renin activity, but also to the standard method of saralasin testing that we evaluated. Although prior sodium depletion of the patients eliminated false-negative responses, therefore improving the validity of the saralasin test as a screening procedure, it did not enhance the test's discriminatory power and increased the overall expense of investigation.

With regard to predicting the prognosis for renal artery bypass surgery, we believe that saralasin testing compares unfavourably with diazoxide-stimulated renal vein renin testing. We have recently reviewed our experiences with the latter technique (MacCarthy and Stokes, 1978), which we have found more accurate in diagnosis than either conventional methods of determining the renal vein renin ratio or saralasin infusion procedures.

Acknowledgements

We thank Dr Charles George and Dr Anthony Burke, Repatriation Hospital, Concord, New South Wales, for referring some of the patients herein, Miss Judy Gain, SRN, for technical assistance and Dr Robert Keenan of Morton-Norwich Products, Norwich, NY, for supplies of saralasin acetate. This project was supported by a grant-in-aid from the National Heart Foundation of Australia.

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Vesicoureteric Reflux with Urethral Valves

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Summary—A retrospective review was undertaken of 66 boys with posterior urethral valves with regard to incidence and prognostic significance of vesicoureteric reflux. The results indicate that:

Regardless of the age of the patient, the existence of bilateral reflux at the time of presentation implies a worse prognosis than does unilateral or no reflux.

Reflux which does not stop spontaneously after the valves have been destroyed is generally associated with a functionless and often dysplastic kidney; surgical cure of such reflux is therefore pointless.

Reflux stops spontaneously after valve ablation when the involved kidney possesses useful function; surgical cure of reflux is therefore unnecessary.

In some cases, however, it remains possible that reflux may continue to damage the kidney during the interval between relief of the urethral obstruction and spontaneous cure of the reflux. Nevertheless, the grossly dilated refluxing ureter is poor surgical material and it is concluded that the best chance of preserving renal function in the majority of boys with urethral valves and reflux lies in endoscopic fulguration of the valves, controlling infection and awaiting spontaneous reflux cure.

Vesicoureteric reflux is a common complication of obstructing posterior urethral valves in boys. However, uncertainty has existed concerning its prognostic significance and its management and diverging views have been expressed. Williams *et al.* (1973) stated that, in their series, reflux was not such a serious complication as had been anticipated and that the mortality was in fact lower in the refluxing group than in the non-refluxing one. Cass and Stephens (1974), on the other hand, recommended that significant reflux persisting after valve ablation should be corrected by an antireflux operation. Williams (1977), reviewing 100 cases of valves with hydronephrosis, found that those with bilateral reflux presented a gloomy picture in the long term. Because of these differing experiences and opinions a retrospective review of a personal series was undertaken.

Patients and Methods

Information was obtained concerning the incidence, effects and natural history of reflux in 66 boys with valves. Follow-up was to the death of the patient or, in the survivors, for periods between 1 and 20 years. In the great majority of patients the initial surgical treatment consisted of endoscopic fulguration of the valves.

Results

Incidence and Prognosis

The occurrence and long-term prognosis of reflux as regards survival are shown in the table. The incidence of bilateral, unilateral and no reflux before surgery was similar in each group but the mortality rates are 57.1%, 17.4% and 9.1% respectively, indicating that the prognosis is worst in the cases with bilateral reflux. The 8 survivors who had bilateral reflux at presentation, and who are now alive and well, each showed spontaneous cure of reflux on one or both sides after the valves were destroyed. In 7 of 12 non-survivors death occurred in spite of the fact that the kidneys had been protected against the effects of reflux by cutaneous ureterostomy or by ureteric reimplantation into the bladder.

It is well recognised that boys with severe renal impairment resulting from valvular urethral obstruction generally present in the first few

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Table Prognosis as Regards Reflux at the Time of Presentation

	Alive and well	*Alive, azotaemic*	*Dead*
No reflux 22	19	1	2 (9.1%)
Unilateral reflux 23	18	1	4 (17.4%)
Bilateral reflux 21	8	1	12 (57.1%)

weeks of life, so that the mortality rate is higher in this group. For this reason the mortality figures were re-analysed to allow for the age at presentation. In boys presenting under the age of 1 month the mortality rates for those with bilateral, unilateral and no reflux were 66.6%, 20% and 14.3% respectively. In those presenting between the ages of 1 month and 1 year and in those presenting over 1 year of age the corresponding figures were 50%, 20% and nil and 33.3%, 12.5% and 10%. It is clear that bilateral reflux existing before surgery carried a poorer outlook than unilateral or no reflux, regardless of the age at presentation.

Spontaneous Cure of Reflux and Kidney Quality

Reflux stopped spontaneously after valve ablation with 30 ureters in 16 patients. Among 9 cases with initially bilateral reflux, cure was bilateral in 4 and unilateral in 5 (Figs. 1 and 2). Eight of these boys survive. In 7 boys unilateral reflux underwent spontaneous cure; all patients survive. Since, in individual patients, cystograms were performed infrequently after valve surgery, the time interval between operation and the cessation of reflux could not be determined precisely; the extremes were within 2 weeks and between 9 and 13 months.

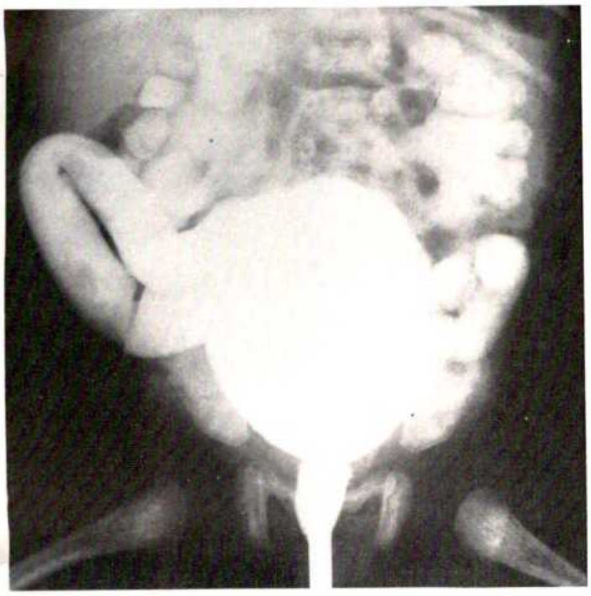

Fig. 1 A.S. Cystogram aged 3 weeks, before surgery. Bilateral reflux to dilated upper tracts.

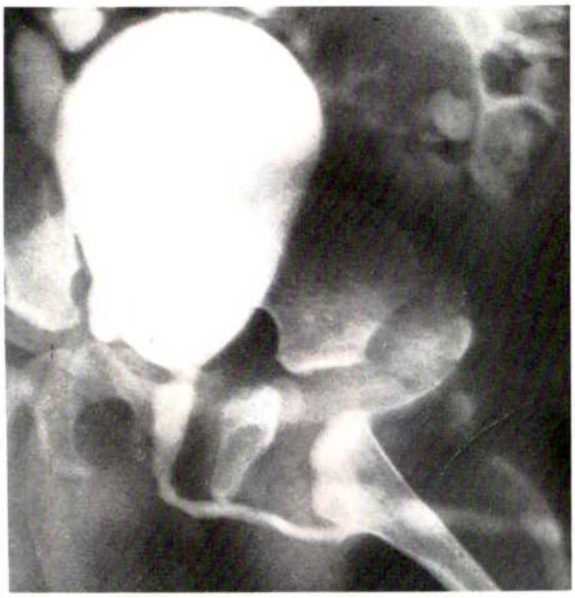

Fig. 2 A.S. Cystogram 6 months after endoscopic valve fulguration. Persistent reflux on right. Reflux on left has stopped spontaneously.

The quality of 19 kidneys to which reflux stopped spontaneously was assessed from the intravenous urograms. In 11 the pyelographic appearance had improved as regards concentration of the medium and also the pelvicaliceal dilatation when compared with previous examinations (Figs. 3, 4 and 5). In 4 kidneys the appearances were unchanged before and after cure of reflux. In 2 boys both kidneys showed deterioration. One of these presented aged 5 weeks with moderate upper tract dilatation and bilateral reflux. The blood urea on admission was 26.2 mmol/l. The urine contained leucocytes + + + but culture produced a non-significant growth. Reflux had stopped 5 months after fulguration of the valves. Subsequent renal growth was impaired and a renal biopsy at the age of 15 months showed an area of infective pyelonephritis. At the age of 11 years the boy is below the third percentile for height and weight. The blood chemistry is normal. Intravenous urography shows that both kidneys are

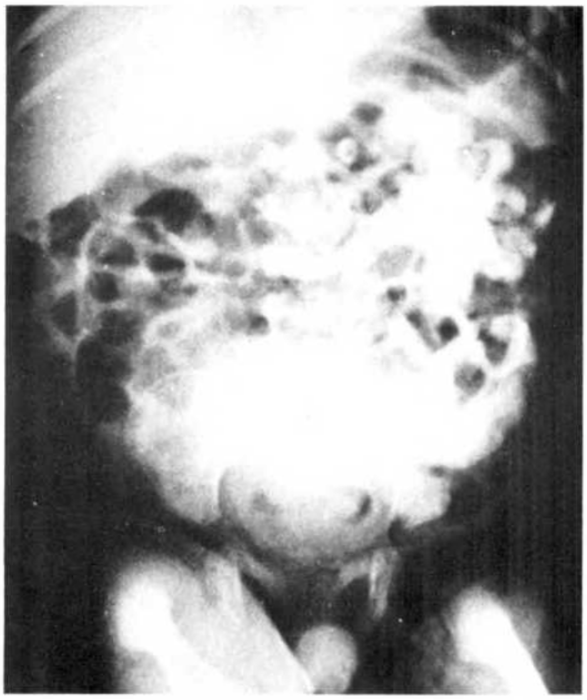

Fig. 3 A.S. Urethral valves. IVP on admission aged 3 weeks. Left hydroureteronephrosis. No concentration by right kidney.

undilated but are small; the right is 7.5 cm long and the left 8.4 cm (mean kidney length at 11 years is 10 cm). The other boy had severe upper tract dilatation and bilateral reflux to hydronephrotic kidneys when admitted at the age of 6 months. The blood urea was then 32 mmol/l. The urine contained pus cells but had antibacterial substances and was sterile. Bilateral reflux was still present 9 months after valve fulguration but had stopped by 13 months. At the age of 2½ years the blood urea ranged from 9.8 to 12.6 mmol/l and the serum creatinine was 110 mmol/l. Intravenous urography showed very poor concentration bilaterally but the upper tract was somewhat less dilated than prior to the cessation of reflux and there was no residual obstruction.

Spontaneous cure of reflux is in some instances precarious and late recurrence may take place. This was seen in 3 boys. In one, reflux recurred bilaterally following partial cystectomy for bladder atony. In another, unilateral reflux recurred after bladder neck reconstruction for urinary incontinence. In the third, reflux to a sole remaining kidney recurred 10 years after its original cessation as a result of involvement of the ureteric orifice in an enlarging bladder diverticulum.

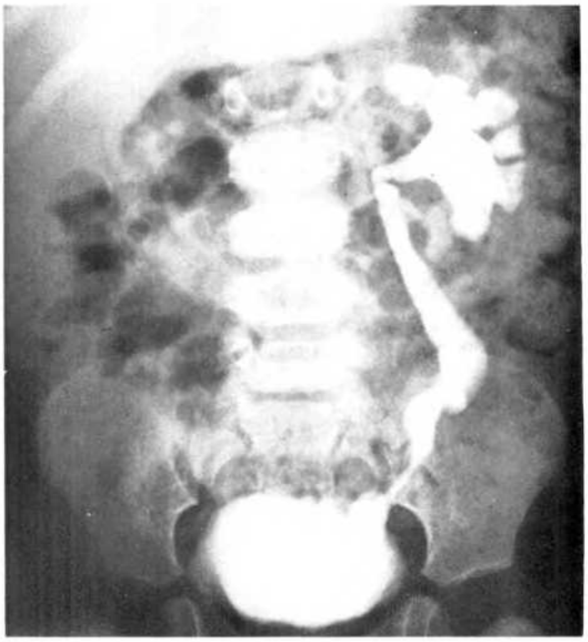

Fig. 4 A.S. IVP 14 months after valve fulguration. Less dilatation of left kidney and ureter. No concentration by right kidney. Right nephroureterectomy performed.

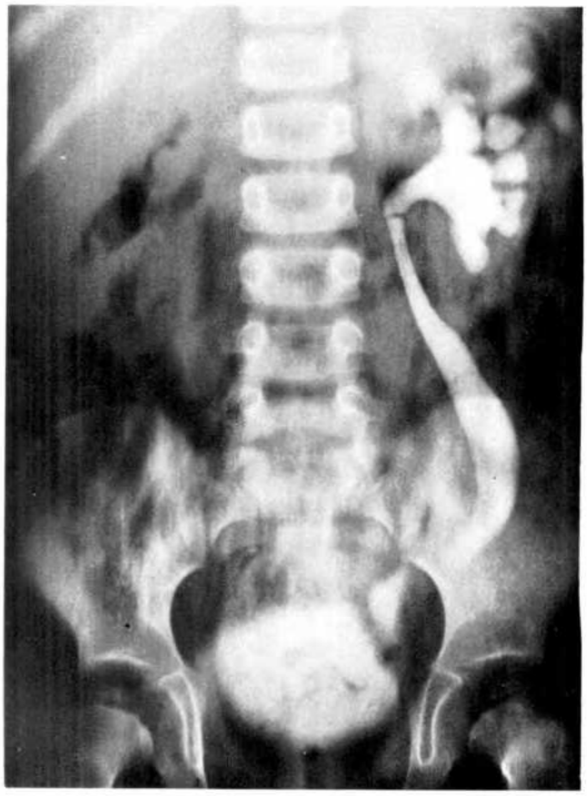

Fig. 5 A.S. IVP 4 years after fulguration of valves. Further improvement of left kidney and ureter.

Persistent Reflux and Kidney Quality

Histology was available from autopsies of 14 kidneys to which reflux persisted after valve ablation. Eight kidneys in 5 patients were grossly dysplastic, being composed of fibrous tissue, small cysts, nests of cartilage and, in some, rudimentary tubules and/or glomeruli. They had obviously never shown any useful function. One kidney in one patient showed localised dysplastic areas. Five kidneys exhibited parenchymal atrophy with fibrosis and infection but without evidence of dysplasia of pre-natal origin. In 18 surviving patients with persistent unilateral reflux the affected kidney was functionless and each patient underwent nephroureterectomy. Fourteen of these kidneys were totally dysplastic (Fig. 6), one had local dysplasia and 3 showed simply atrophy and fibrosis.

Discussion

The present review indicates that, whilst obstruction alone can cause severe upper tract dilatation and renal functional impairment in boys with urethral valves, obstruction and reflux are much more damaging; thus the prognosis for patients with bilateral reflux before surgery is significantly worse than for those with unilateral or no reflux, regardless of the age at presentation.

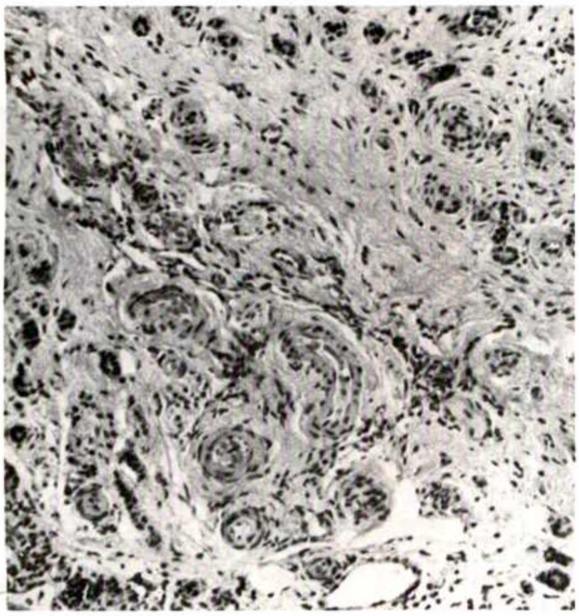

Fig. 6 A.S. Histology of dysplastic right kidney (×50). Primitive tubules and glomeruli.

As regards management, 2 inferences may be drawn from the series. First, when reflux exists prior to valve ablation but the affected kidney has useful function, the reflux will stop spontaneously when the obstruction has been relieved. There is therefore no need for surgical cure of reflux. Second, reflux which persists after the valves are destroyed is associated with a non-functioning and generally dysplastic kidney, so that operative cure of reflux is pointless. However, these conclusions over-simplify the matter since they beg the question as to what is meant by persistent reflux. We do not know how long reflux can continue after the elimination of the urethral obstruction yet still stop spontaneously; in the present series the maximum period was between 9 and 13 months. It is possible that reflux which continues after valve ablation, even if only for a short time and even if infection is controlled, may continue to damage the kidney. Assessment of the likelihood of this occurrence is hindered by the difficulties which exist in performing and interpreting measurements of renal function, particularly of the individual kidney, in babies and young children. In the present series, where changes in kidney function were determined from repeated pyelography and blood chemistry estimations, improvement was evident in 11 kidneys following the spontaneous cure of reflux and the situation appeared unchanged in 4. In 2 boys in whom reflux cured itself, 4 kidneys showed deterioration, but it was impossible to decide precisely when the renal damage was inflicted.

Reconstruction of the upper urinary tract with urteric shortening, narrowing and reimplantation to the bladder has been advocated in the management of boys with urethral valves (Hendren, 1970). In my experience this therapy can be effective when there is no reflux since non-refluxing hydroureters generally retain, or can regain, effective peristaltic function. However, in the absence of an unequivocal obstruction at the ureterovesical junction (Whitaker, 1973), surgery of this type is unnecessary since the kidneys and ureters are capable of marked spontaneous improvement following simple valve ablation (Johnston and Kulatilake, 1971). The extremely dilated refluxing ureter, on the other hand, gives much less satisfactory results following ureteric tailoring and reimplantation since its peristaltic activity is generally severely, and often irreversibly, impaired. Even in the absence of any technical error or complication, dilated refluxing ureters are readily obstructed by surgery since the hypoactive pelvis and upper ureter may be incapable of overcoming the increased, but not abnormal, resistance in the ureteric segment narrowed by operation (Johnston and Farkas, 1975).

It is concluded that, in the boy with urethral valves and reflux to functioning kidneys, the best chance of preserving renal function lies in relieving the urethral obstruction by endoscopic fulguration of the valves, controlling infection and awaiting spontaneous cure of the reflux. Operative intervention on the ureters in the form of either temporary ureterostomy or tailoring and reimplantation is needed only if there is clinical, bacteriological, biochemical, radiographic or other evidence that renal damage is progressing.

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End-to-end Ureteroileal Anastomosis for Ileal Conduits

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Summary—In the "Y" anastomosis, both ureters are spatulated and joined together to form a single tube which is anastomosed to the proximal end of the ileum.

This technique has several theoretical advantages which appear to be borne out in practice when the results of its use in 101 patients followed for up to 12 years are reviewed.

Only 2 anastomotic leaks needed operative treatment and only 4 patients developed ureteroileal stenosis. Renal function remained unchanged or improved in 84% of the patients, and definite hydronephrosis or pyelonephritis developed in only 4% of the kidneys.

These results show that this method of ureteroileal anastomosis is at least as good as, and possibly better than, other techniques.

In the ileal conduit first described in 1950 by Bricker, the proximal end of the conduit was closed and the ureters anastomosed separately end-to-side. Although the ileal conduit had many advantages over previous methods of urinary diversion, renal function sometimes deteriorated. Bricker *et al.* (1954), in their careful study of 65 of the first 106 ileal conduit patients, found definite hydronephrosis or pyelonephritis in 30%, sometimes dating from before the diversion but often developing afterwards. Different modifications of the ureteroileal anastomosis have been suggested to minimise these complications, and those in which the ureters are anastomosed to the proximal end of the conduit are considered in this review (Fig. 1).

Wallace (1966) spatulated the ureters and sewed their medial borders together before anastomosing them to the proximal end of the conduit. Later, because ureteric obstruction had sometimes followed this method, he advocated sewing the ureters head-to-tail instead of side-to-side (Wallace, 1970).

The late Mr F. P. Raper of Leeds sometimes sewed both borders of the spatulated ureters together and anastomosed this single tube to the conduit. He described this method to me in 1964 and I have used it continuously ever since. Wendel *et al.* have also used it and in 1969 published a preliminary report of satisfactory results in 7 patients followed for up to 18 months. This report describes the technique of the "Y" anastomosis and the results obtained in a personal series of 101 patients followed for up to 12 years.

Patients and Methods

Between October 1964 and December 1976, 101 ileal conduits were constructed using the "Y" anastomosis.

Sixty-six patients were male and 35 female. Twenty-four had benign conditions and 77 malignant conditions. The age range is shown in Table 1 and the indications for operation in Table 2.

A window is cut in the posterior peritoneum in front of the bifurcation of the aorta and the cut ends of the ureters brought through this window, taking care to avoid obstruction. The ends are spatulated for 2 to 3 cm (Fig. 2). The medial borders of the spatulated ureters are sewn together with a continuous stitch. A bulb-ended catheter is passed up each ureter, then the stitch is continued around the upper ends of the spatulations, and the lateral borders sewn together to

Table 1 Age Range for Benign and Malignant Conditions

Age	*0-9*	*10-19*	*20-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70-79*
Benign	5	9	4	–	1	3	1	1
Malignant	–	–	–	3	6	14	43	11
Total	5	9	4	3	7	17	44	12

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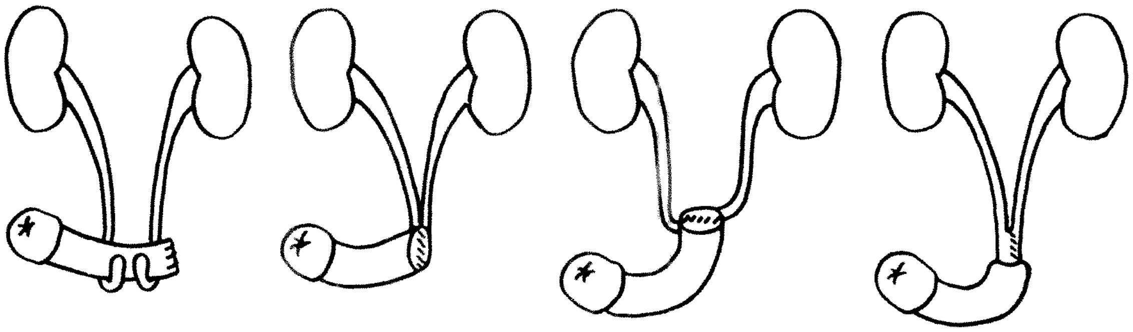
Bricker 1950 Wallace 1966 Wallace 1970 'Y' Anastomosis

Fig. 1 Methods of ureteroileal anastomosis.

produce a single tube. The catheters are then withdrawn to demonstrate that there is no obstruction at the upper ends of the spatulations. The single ureteric tube is anastomosed end-to-end to the proximal part of the conduit and the distance between the stitches in ureter and ileum adjusted to correct any disparity in diameter (Fig. 3). With ureters of normal calibre, the diameter of the ileum will be twice that of the joined ureter, so that the width between sutures in the ileum must be twice as wide as between those taken in the ureter. After completion of the anastomosis the cut edges of the window in the posterior peritoneum are sewn to the conduit just in front of the ureteroileal junction (Fig. 4). This makes the anastomosis retroperitoneal and prevents any tension by anchoring the ileum securely. The anastomosis is not splinted. When the ileal conduit follows cystectomy the pelvis is drained; otherwise drainage is not usually employed.

Table 2 Indications

Benign conditions		24
Incontinence		22
Spina bifida	13	
Epispadias	1	
Ureterocolic anastomosis	3	
Other causes	5	
Other conditions		2
Neurogenic bladder—reflux pyelonephritis		
Interstitial cystitis—contracted bladder		
Malignant conditions		77
Cystectomy for carcinoma of the bladder		67
Anterior exenteration for carcinoma of cervix		2
Palliative for various tumours		8

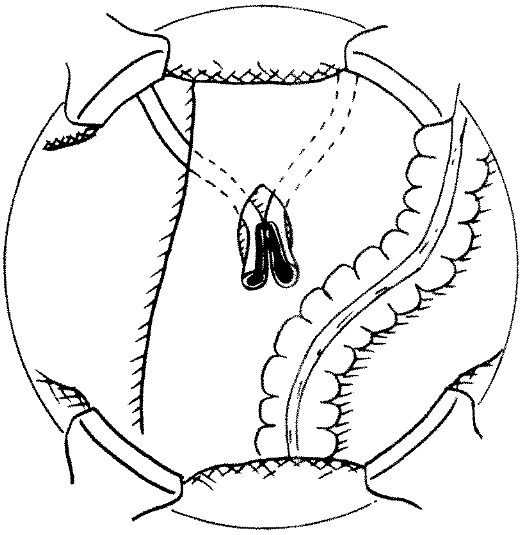
Fig. 2 Ureters brought through window in posterior peritoneum and spatulated.

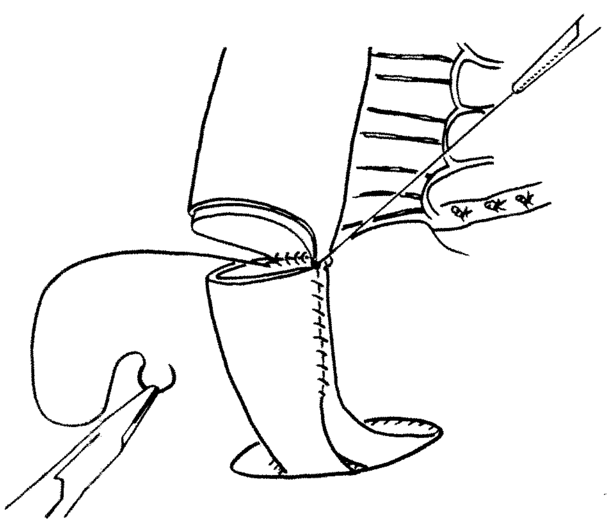
Fig. 3 Single ureteric tube anastomosed end-to-end to conduit.

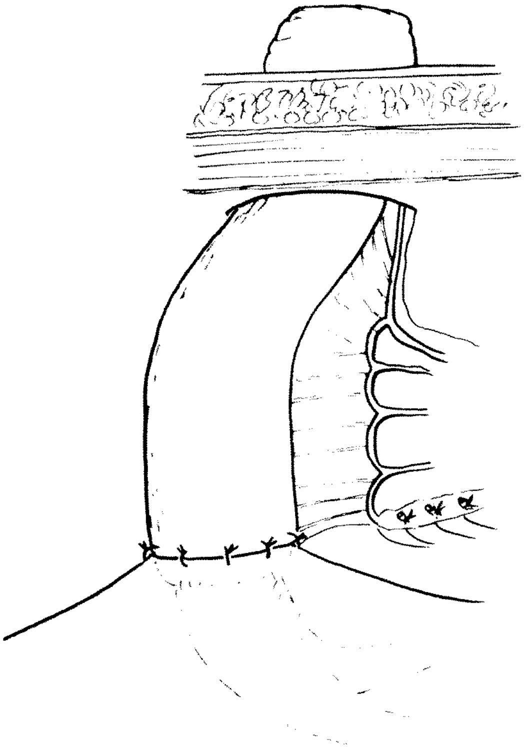

Fig. 4 Edge of window in peritoneum sewn to ileum in front of anastomosis.

Results

Operative Mortality

Eight of the 101 patients who had an ileal conduit with a "Y" anastomosis died in the immediate post-operative period. The causes of death are listed in Table 3. In no patient could death be ascribed to complications from the ileal conduit or the "Y" anastomosis.

Follow-up

The 93 patients who left hospital were seen every 6 months to detect complications. The stoma was inspected since encrustation has been found to be a sign of a poor blood supply and impending stenosis (McEwan and Clark, 1973). The blood urea and, since 1970, the serum creatinine, were usually measured. Intravenous urography was usually performed 3 months after diversion and thereafter every 2 years.

The cases were analysed in December 1977. This allowed a minimum period of follow-up of 1 year; the maximum was 12 years. The average period of follow-up was 3 years 7 months.

Table 3 Operative Mortality—Causes of Death

After cystectomy	pulmonary embolus left ventricular failure inhaled vomit myocardial infarction cardiac arrest congestive cardiac failure
After palliative diversion	multiple fistulae
Conversion from rectal bladder	volvulus of splenic flexure

Table 4 Late Mortality—Causes of Death

Carcinomatosis	36
Renal failure	5
Unrelated causes	4
Unknown	5
	50

Survival and Causes of Death

Forty-three patients were alive in December 1977. In addition to the operative deaths, 47 patients were known to have died; 3 were lost to follow-up and are presumed dead (Table 4).

Post-operative Complications

Seven of 10 post-operative complications were associated with the ileal conduit and only 2 of these were associated with the "Y" anastomosis —the 2 cases of ureteroileal leakage (Table 5).

Late Complications

Nineteen patients had late complications; 1 patient had 3 separate complications (Table 6). Seventeen

Table 5 Post-operative Complications

Ileal conduit		*Cystectomy*	
Intestinal obstruction	3	Acute tubular necrosis	1
Intestinal leak	1	Faecal fistula/lung abscess	1
Ureteric obstruction	1	Osteitis pubis	1
Ureteroileal leak	2		
	7		3

Table 6 Late Complications

Ileal conduit		*Other complications*	
Stomal stenosis	7	Pyocystis	1
Stenosed conduit	1	Pelviureteric obstruction	1
Renal stones	4	Intestinal obstruction	1
Hernia alongside stoma	1	Faecal fistula	1
Ureteroileal stenosis	4		
	17		4

Table 7 Renal Function

Pre-operative		*Post-operative*		
Blood urea	*Patients*	*Improved*	*No change*	*Worse*
0-7.1 mmol/l	72	–	63	9
7.1-17 mmol/l	10	4	3	3
Over 17 mmol/l	2	1	–	1
	84	5	66	13

Table 8 Urographic Findings

Pre-operative		*Post-operative*				
	Grade	*1*	*2*	*3*	*4*	*5*
Normal kidney	1	65	23	3	–	–
Minimal hydronephrosis	2	5	5	–	–	–
Definite hydronephrosis	3	6	4	9	–	–
Massive hydronephrosis	4	1	–	–	2	–
Non-function	5	1	3	–	–	1
		78	35	12	2	1

were associated with the ileal conduit; those associated with the "Y" anastomosis were the 4 cases of ureteroileal stenosis.

Renal Function

Estimations of blood urea were performed on 84 patients post-operatively and compared with the pre-operative levels (Table 7). There was no change in renal function in 66 patients, an improvement in 5 and deterioration in 13. Thus renal function remained unchanged or improved in 84% of patients during the period of follow-up.

Urography

Intravenous urography was performed on 77 patients post-operatively and in 63 it could be compared with the pre-operative findings (Table 8). The urograms have been graded according to the method used by Bricker *et al.* (1954): normal; minimal, definite or massive hydronephrosis; non-function. One patient had bilateral duplex ureters—one on each side a megaureter—so that there is a total of 128 kidneys.

In Table 8 the diagonal across the square represents no change; figures to the left of the diagonal represent improvement, those to the right deterioration. In addition, two previously normal kidneys became pyelonephritic. Thus definite hydronephrosis or pyelonephritis developed in only 4% of the kidneys studied.

Discussion

The "Y" anastomosis has the following theoretical advantages: it produces an uninterrupted, peristaltic tube; there are no kinks, no pouches and no blind loops; the spatulation of the ureters reduces the risk of stenosis; it is retroperitoneal; no tension can fall on it because the ileum is anchored; it can be used with dilated ureters or those of normal calibre.

Does it have any practical advantages? To decide this the results of the "Y" anastomosis must be compared with the results of other methods of ureteroileal anastomosis.

It is difficult at present to compare it with other methods of anastomosing the ureters to the proximal end of the conduit. Wallace (1966) reported 3 cases of ureteroileal leakage in 100 patients in whom he had used his first method of

Table 9 Results After Ureteroileal Anastomosis

	No. of patients	*Ureteroileal leakage*	*Ureteroileal stenosis*	*Renal function unchanged*	*Urography*	
					Kidneys	*Deterioration*
Bricker anastomosis						
Burnham and Farrer, 1960	96	14 (14.5%)	12 (12.5%)	–	–	–
Bowles *et al.*, 1964	278	–	19 (6.7%)	–	–	–
Jaffe *et al.*, 1968	543	5 (1%)	20 (3.9%)	–	–	–
Harbach *et al.*, 1971	244	14 (5.7%)	16 (7.9%)	–	–	–
Schmidt *et al.*, 1973	178	4 (2.2%)	14 (7.8%)	82%	–	–
Gregory *et al.*, 1974	81	–	–	–	156	12%
Shapiro *et al.*, 1975	90	–	20 (22.3%)	–	144	18%
Hensle *et al.*, 1976	1120	21 (1.87%)	–	–	–	–
"Y" anastomosis	101	2 (2%)	4 (4%)	84%	156	4%

anastomosis; in 1970 he reported that he had abandoned this method because some patients had developed ureteric obstruction; after a year's experience with his second method of anastomosis no leakage had occurred, but there are no published data on a large series of cases or after prolonged follow-up.

The "Y" anastomosis can only be compared in detail with the original Bricker anastomosis and this is done in Table 9. The results obtained with the "Y" anastomosis appear to be almost as good as the best obtained with the Bricker operation, and better than many reported series. Perhaps this is because the "Y" anastomosis avoids urinary stasis, as suggested by Derrick and Hodges (1972).

Two other points deserve brief mention—splints and reflux. Wallace (1966, 1970) used splints for his anastomoses. None are used with the "Y" anastomosis. Richie *et al.* (1975), in a comparative series, found a higher incidence of urinary leakage when "stents" were used. Reflux occurs freely across the "Y" anastomosis; no attempt is made to prevent it. Bricker used a Cordonnier technique, which also allows free reflux, and even when a Leadbetter or nipple anastomosis has been used reflux can be demonstrated in half of the patients studied (Mount *et al.*, 1968; Kafetsioulis and Swinney, 1970). The results obtained support Bricker's concept of the ileum functioning as a conduit to transmit urine as quickly as possible to the bag of the appliance, which is the equivalent of the bladder. However, the long-term significance of reflux is unknown.

Care must be taken in joining the ureters together and in joining them to the ileum. The results of any surgical procedure depend upon its basic design and upon the care taken in performing it. No greater care is necessary in constructing a "Y" anastomosis than in performing a pyeloplasty. Bricker and his colleagues introduced the ileal conduit to overcome the problems of urinary diversion after pelvic evisceration. What more suitable ending could there be than this quotation from Bricker's original article?

> "It is obvious that the technic of anastomosing the ureters to the intestine is an integral part of the procedure of pelvic evisceration. We firmly believe that the end results of this type of surgery will depend very largely on the technic and care with which this anastomosis is done."
>
> Bricker (1950)

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Urinary Incontinence in the Female. The Value of Detrusor Reflex Activation Procedures

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Summary—One hundred consecutive female patients with urinary incontinence were investigated with CO_2 cystometry including detrusor reflex activation procedures such as postural change and ability to suppress self-induced detrusor contractions.

Detrusor hyperreflexia was seen in 20 patients during bladder filling in the supine position, and in an additional 35 patients after detrusor reflex activation procedures. Four different types of detrusor hyperreflexia are described based on the cystometric findings. In 38 patients treated with parasympatholytics, 66% showed a good result independent of the type of detrusor hyperreflexia.

The incidence of detrusor hyperreflexia in women with urinary incontinence varies from 10 to 50% (Hodgkinson *et al.*, 1963; Arnold *et al.*, 1973; Walter, 1978). Using rapid fill CO_2 cystometry, including detrusor reflex activation procedures as a routine, we found that the incidence of detrusor hyperreflexia increased significantly compared with previously used medium fill water cystometry. This prompted us to evaluate in retrospect the cystometric findings in 100 consecutive female patients with urinary incontinence.

Material and Methods*

One hundred consecutive incontinent female patients referred for cystometry from October 1976 to October 1977 were studied. Fifty-seven patients were referred from the local departments of gynaecology or urology, where all patients complaining of urinary incontinence underwent routine cystometry. The remaining patients were referred from other hospitals. Seventeen patients had had one or more previous operations for incontinence. Thirty-seven patients had stress incontinence, 20 patients urge incontinence, while the rest claimed to have both stress and urge incontinence. The mean age was 51 years with a range from 18 to 90 years.

Cystometry was performed with CO_2 as filling medium at a filling rate of 200 ml per min through a transurethral 18 FG Foley catheter. Urethral sphincter electromyography was routinely recorded with a ring electrode mounted on the catheter (Nordling *et al.*, 1978a). Cystometry was first performed with the patient in the supine position. The patient was asked to indicate when the first sensation of fullness was felt and was instructed to suppress micturition during filling of the bladder. The volume at which the patient felt uncomfortable or had bladder pain was registered as the cystometric bladder capacity. At this volume the CO_2 flow was stopped and the patient instructed to cough. After coughing the patient was asked to void without straining. If a detrusor contraction was elicited, the patient was again instructed to suppress micturition and the intravesical pressure normally decreased to pre-voiding level within 50 s (Fig. 1). After emptying the bladder, the cystometric procedure was repeated with the patient standing.

According to the cystometric findings the patients were classified as follows (Table 1):

All patients showing uninhibited detrusor contractions during filling were classified as detrusor hyperreflexia Type 1 (Fig. 2). Patients without uninhibited detrusor contractions but unable to suppress a self-induced detrusor contraction within 50 s were classified as detrusor hyperreflexia Type 2 (Fig. 3).

Patients demonstrating detrusor hyperreflexia in the supine position were classified as Type 1A or Type 2A, whereas patients first demonstrating

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* Methods, definitions and units conform to the standards proposed by the International Continence Society except where specifically noted.

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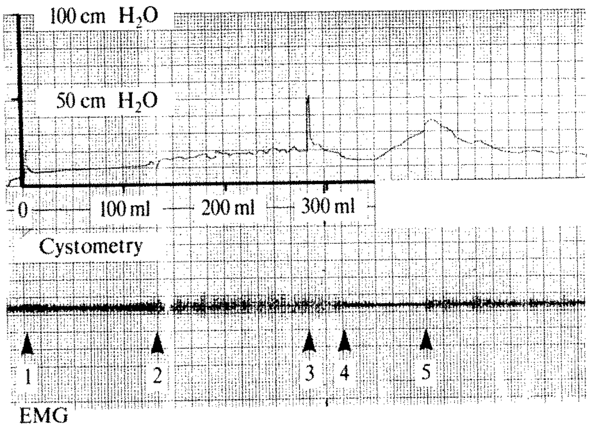

Fig. 1 Normal cystometry. (1) Start of bladder filling. (2) First sensation of fullness. (3) Patient coughing followed by cessation of bladder filling. (4) Patient asked to void. EMG activity ceases completely. (5) Patient asked to inhibit voiding.

detrusor hyperreflexia in the standing position were classified as Type 1B or 2B.

All patients were further evaluated with vaginal examination and micturition cystourethrography in the straight lateral projection (Olesen and Walter, 1977). If the patient claimed to have urgency, cystoscopy was performed.

Patients with detrusor hyperreflexia were primarily treated with the anticholinergic drug Cetiprin® (emepronium bromide 200 mg qid), unless they had prevailing symptoms from genital prolapse, which was treated surgically.

The effect of pharmacological treatment was subjectively estimated after 1 month of therapy.

Results

Detrusor hyperreflexia was found in 55% of the patients (95% confidence limits 44-65%). The frequency of the different types is outlined in Table 2. Eleven of the patients with detrusor hyperreflexia had stress incontinence, 14 urge incontinence and the rest both stress and urge incontinence. Eleven patients were primarily submitted for surgery; 9 had genital prolapse, 1 had a urethral diverticulum and 1 had a urethral stricture.

In 5 patients the incontinence was so slight that treatment was not indicated; 3 of these

Table 1 Classification of Detrusor Hyperreflexia. Patients Unable to Suppress a Self-induced Detrusor Contraction in the Supine Position and having Uninhibited Detrusor Contractions in the Standing Position were Classified as Type 1B

	Supine	*Standing*
Uninhibited detrusor contractions during filling	Type 1A	Type 1B
Inability completely to suppress self-induced detrusor contraction	Type 2A	Type 2B

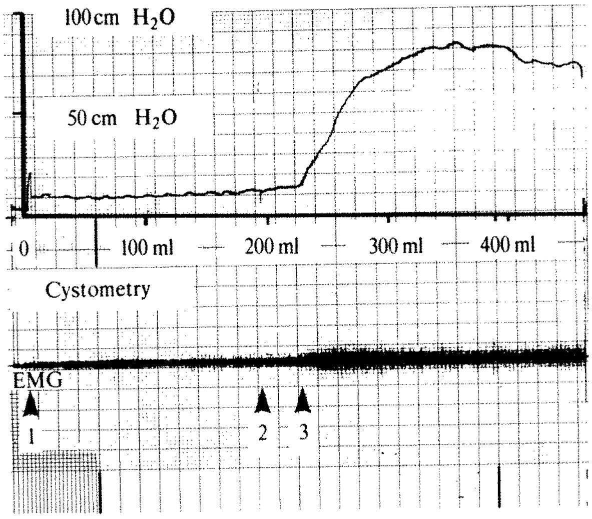

Fig. 2 Detrusor hyperreflexia Type 1A. (1) Start of bladder filling. (2) First sensation of fullness. (3) Uninhibited detrusor contraction begins at bladder volume of 200 ml. The high EMG activity indicates that the patient tries to inhibit voiding.

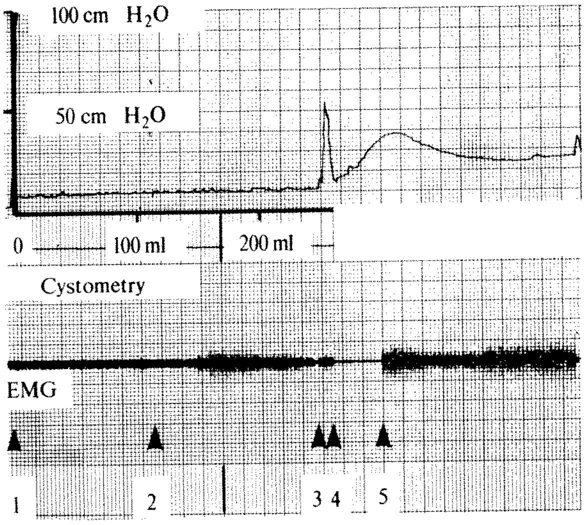

Fig. 3 Detrusor hyperreflexia Type 2A. (1) Start of bladder filling. (2) First sensation of fullness. (3) Patient coughing followed by cessation of bladder filling. (4) Patient asked to void. EMG activity ceases completely. (5) Patient asked to inhibit voiding but bladder pressure only decreases to 24 cm H_2O, although pre-voiding pressure was only 10 cm H_2O.

Table 2 Cystometric Finding of Detrusor Hyperreflexia in 100 Consecutive Female Patients with Urinary Incontinence

		Number of patients
Detrusor hyperreflexia	Type 1A	20
	Type 2A	6
	Type 1B	22
	Type 2B	7
Detrusor hyperreflexia total		55

patients had detrusor hyperreflexia Type 1A and 2 Type 1B.

One patient with trigonitis diagnosed at cystoscopy was cured after bladder instillations of silver nitrate 0.2%.

The remaining 38 patients were treated with emepronium bromide 200 mg qid (Table 3). In patients receiving therapy for at least 1 month we found an overall improvement rate of 66% (95% confidence limits 48-81%). In groups 2A and 2B, where the patients showed no uninhibited detrusor contractions but only inability to suppress the self-induced detrusor contraction within 50 s, the improvement rate was 88% (95% confidence limits 47-100%). Two patients with detrusor hyperreflexia Type 1B and no effect with emepronium bromide were later cured, one by oestrogen therapy and one after colposuspension.

Side effects of treatment with emepronium bromide were rather common and necessitated discontinuation of the drug within a few days in 2 patients and after more than 1 month in 3 patients. The side effects were mainly well known parasympatholytic side effects, most often disturbance of eye accommodation. One patient had to give up medication because of severe pain in the lumbar region, which disappeared after discontinuation of the drug and returned on resumption.

Discussion

The finding of deficient control of detrusor reflex contraction in 55% of female patients with urinary incontinence is rather high in comparison with previous cystometric studies in such patients (Hodgkinson *et al.*, 1963). In a prospective study of 303 patients using medium fill water cystometry in the supine position (Walter, 1978), detrusor hyperreflexia was found in 15% of the patients. It has been shown that medium fill water cystometry and rapid fill CO_2 cystometry have the same diagnostic specificity (Nordling *et al.*, 1978b), so it seems unlikely that the different filling medium and filling rate are responsible for the difference. On the other hand, the technique used by Walter revealed only the type of detrusor hyperreflexia described in this paper as detrusor hyperreflexia Type 1A. We found Type 1A in 20%, which is in accordance with Walter. The same incidence was found by others, 18% (Arnold *et al.*, 1973) and 29% (Arnold, 1974), during filling cystometry in the supine position. Therefore the higher frequency found in this study is ascribed to the use of detrusor reflex activation procedures and the testing of the patient's ability to suppress self-induced detrusor contraction. A frequency of detrusor hyperreflexia of 55% corresponds well to the frequency of detrusor instability of 48% found by Arnold *et al.* (1973) and 71% by Arnold (1974).

The significance of the inability to suppress a self-induced detrusor contraction within 50 s is indicated by the good results of treatment with parasympatholytics in patients not presenting uninhibited detrusor contractions during bladder filling (Types 2A and 2B).

The finding of detrusor hyperreflexia in more than half of the female patients with urinary incontinence means that many patients will present with bladder suspension defects as well as detrusor hyperreflexia.

In these cases either drug treatment or surgical treatment might be considered. In the past we have been very reluctant to operate on patients with detrusor hyperreflexia. This might be due to the many patients seen who had already undergone numerous unsuccessful surgical procedures before cystometric investigation revealed detrusor hyperreflexia. However, these poor results do not preclude the possibility that patients having both detrusor hyperreflexia and bladder suspension defects might benefit from an operation. On the other hand, to operate on patients with detrusor hyperreflexia demands very reliable methods of

Table 3 Primary Treatment of 55 Patients with Detrusor Hyperreflexia

Parasympatholytics	38
Surgery	11
No treatment	5
Bladder instillation of silver nitrate 0.2%	1
Total	55

diagnosing bladder suspension defects, and in this respect we find micturition cystourethrography in the lateral projection to be indispensable.

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The Effect on Erection and Orgasm of Cystectomy, Prostatectomy and Vesiculectomy for Cancer of the Bladder: A Clinical and Electromyographic Study

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Summary—Forty-three men who had been subjected to cystectomy and concomitant prostatectomy, vesiculectomy and urethrectomy were interviewed about their pre-operative and post-operative sexual activities at a mean of 3 (range 1 to 8) years after operation.

Twenty-eight of the 38 men (74%) who had been sexually active continued to have some form of sexual activity, 21 of them achieving orgasm. Only 3 men had penile erection; 2 of them had been subjected to prostatectomy and 1 to prostatic resection. One of these men treated by prostatectomy had also had urethrectomy.

Electromyographic registration from the striated external urethral sphincter, the bulbocavernosus muscle and the levator ani muscle showed normal duration of muscular contractions and length of interval between contractions after operation. The pattern of impulses during orgasm did not differ from that of normal men.

Disturbances of erection, ejaculation, and orgasm have been described after surgical procedures in the pelvis. Following rectal extirpation for benign conditions, erection or ejaculation is affected in up to 20% of the cases (Stahlgren and Ferguson, 1958; Watts *et al.*, 1966; Hedlund *et al.*, 1969). Excision of the rectum for cancer is complicated by loss of erection in 35 to 100% (Gabriel, 1950; Goligher, 1951; Watson and Williams, 1952; Bernstein and Bernstein, 1966). After total prostatectomy for cancer, the ability to obtain an erection occurs only in exceptional cases (Ormond, 1947; Scott and Boyd, 1969; Young and Bohne, 1972). The effect on erection and orgasm of cystectomy and prostatectomy for urinary bladder cancer has been discussed by Romanus (1948), who found 2 men out of 7 to have unchanged or only slightly impaired sexual function.

The present study concerns the consequences on male sexual activity of cystectomy with concomitant prostatectomy and vesiculectomy. Three patients were also subjected to urethrectomy. The effect on the myoelectrical activity accompanying orgasm was studied by electromyographic investigation.

Patients and Methods

All patients selected for the study were men without signs of metastases, who had been subjected to total cystectomy without lymph node dissection for cancer of the urinary bladder between January 1963 and March 1973. The follow-up started in April 1974 and comprised 43 men with urinary diversion by cutaneous ureteroileostomy. The pre-operative and post-operative sexual activities of these patients were appraised from 1 to 8 (mean 3) years post-operatively. All interviews were performed by the same physician (B.B.). The primary statements were checked at subsequent routine visits. In most cases the sexual partner was also interviewed. One married man was excluded because of unclear statements from man and wife concerning the sexual ability of the husband. The mean age of the remaining 42 men was 62.3 years (range 29 to 73).

Total cystectomy, vesiculectomy and prostatectomy had been performed in 41 men; one additional patient had a cystectomy, vesiculectomy and a resection of the prostate so that the apical part of the prostate was preserved. Pelvic lymph node dissection or removal of the lymph nodes along the iliac vessels, the inferior vena cava or the aorta was not performed in any patient. Three patients had also been subjected to total ureth-

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rectomy through a perineal, transverse incision behind the scrotum on the same occasion as the suprapubic cystectomy. The bulbocavernosus muscles were separated through a midline incision. The urethra with the corpus spongiosum was completely removed except in the glans penis where only the urethral mucosa was excised.

Physiological Aspects

Different parts of the nervous system control erection, emission, ejaculation and detumescence.

Erection is effected by mental stimulation via the sympathetic hypogastric nerves. In animal experiments these nerves have been shown also to carry cholinergic fibres, which effect dilation of the arteries of the corpora (Bacq, 1935; Root and Bard, 1947). Erection can also be initiated through impulses mediated in the pudendal nerves from the skin sensory fibres of the penis (Bell, 1972; Weiss, 1972). The sensibility of the glans penis is mainly subserved by the second sacral nerve (Bohm *et al.*, 1956; Gunterberg and Petersén, 1976). Via a sacral reflex arc S2, S3 and S4, efferent impulses are mediated through the pelvic nerves (*Nn. erigentes*), which carry parasympathetic, cholinergic impulses responsible for active dilatation of the arteries of the 3 corpora. The pudendal nerves probably cause contraction of the bulbocavernosus and ischiocavernosus muscles together with the striated pelvic floor muscles. The functional and neural mechanisms at *emission* of sperm into the prostatic urethra are effected by the adrenergic sympathetic hypogastric nerves, the impules emanating from the thoracic and upper lumbar segments (T11-L2) (Hotchkiss, 1970) and sympathetically regulated secretion of adrenalin from the adrenals.

Ejaculation and emission are reflex actions, mainly induced from the genital organs, with afferent impulses via the somatic pudendal nerves (S2, S3, S4) and efferent impulses along the same nerves clonically to contract the pelvic floor and perineal muscles (Hotchkiss, 1970). To some extent, these reflexes can be controlled by increasing and reducing the intensity of the stimulation; once brought into action, however, they cannot be influenced by will.

Detumescence is a sympathetic mechanism effected by arterial constriction (Semans and Langworthy, 1938).

Orgasm is not identical with ejaculation and is rather difficult to define. Orgasm can be regarded as the total amount of events at the climax.

Experimental Method

Electromyographic registration of the muscular activity during masturbation was performed in 8 patients who were sexually active post-operatively. The patient was placed in a modified lithotomy position. The EMG was recorded by means of coaxial needle electrodes (0.5 mm outer diameter) which were inserted percutaneously into the muscles according to Kollberg *et al.* (1962) and Petersén and Stener (1970).

The positioning of the needles was monitored by an oscilloscope and a loud-speaker connected to the electromyograph. A 3-channel type of Disa electromyograph was used for registration. When the electrodes were in place, the subject was left alone to bring about orgasm or ejaculation by masturbation. The myoelectric signals of the striated urethral sphincter muscle, the bulbocavernosus muscle and the levator ani muscle were recorded before and during masturbation which, if possible, continued to orgasm.

Statistical Methods

The chi-square, fourfold table (Documenta-Geigy), and Wilcoxon-Mann-Whitney Rank Sum tests were used for statistical calculations.

Results

Interview Study

Thirty-eight of the 42 men had had coitus regularly within 6 months prior to surgery. They all considered their pre-operative sexual function to have been quite normal. The sensation of orgasm had been fully experienced and the erection had been sufficient to perform coitus. Four men (58, 60, 65 and 69 years of age) had been sexually inactive before operation. None of them had attempted to perform coitus since the operation (Table).

Post-operatively, 28 patients (mean age 64.4 years; range 29 to 73) tried to continue with sexual activity, 26 of them with the same partner, while 2 established new sexual contacts. Ten men (mean age at operation 61 years; range 51 to 69; at the interviews 64 years) had not attempted to resume sexual activity after the operation.

Only 3 patients were able to have penile erection after cystectomy. Two of them (29 and 61 years

Table Occurrence of Sexual Activity Pre-operatively and Post-operatively in 42 Men Subjected to Cystectomy, Vesiculectomy and Prostatectomy (41) or Cystectomy, Vesiculectomy and Partial Resection of the Prostate (1)

Age	*N*	*Coitus pre-operative*	*Coitus post-operative*	*Masturbation post-operative*	
				With orgasm	*Without orgasm*
<50	3	3	1	2	0
50-59	9	8	0	6	1
60-69	23*	21*	2*	7*	5
>70	7	6	0	3	1
	42	38	3	18	7

* Partial resection of the prostate.

of age) had been operated upon by prostatectomy and one by prostatic resection (65 years old). The 29-year-old man had also had a urethrectomy. Both he and the 65-year-old man with prostatic resection had occasional spontaneous nocturnal and morning erections. Neither during the morning erections nor at intercourse did they achieve stiffening of the glans during penile erection. All of them responded with penile erection to tactile as well as mental stimulation and had coitus regularly. One man reported short episodes of penile stiffening during orgasm returning 18 months after cystectomy.

Although the remaining 24 patients were sexually active, they did not have a normal erection after the operation. Some of the men who achieved orgasm by masturbation reported a sensation of erection during orgasm.

Twenty-one of the 28 men (mean age 62 years; range 29 to 73) who post-operatively had been sexually active achieved orgasm. Seven men (mean age 63 years; range 56 to 73) did not achieve orgasm.

The 3 who had erection and were able to perform intercourse considered the sensation during orgasm to be unchanged post-operatively. Fifteen men (mean age 57 years; range 41 to 73) of the remaining 18 who achieved orgasm by masturbation stated that the degree of sexual satisfaction was unchanged, while 3 men (58, 70 and 73 years of age) experienced considerable impairment.

In this study the regularity of sexual activity was equally high in ages above and below 60 years. There was no difference in age between the men who had post-operatively ceased and those who continued with sexual activity (Wilcoxon's Test).

Three men had had total urethrectomy; 2 of them experienced normal orgasm post-operatively. The third man was not sexually active prior to or following surgery.

As a rule, the patients who post-operatively achieved orgasm succeeded at the first attempt, which was usually performed from 3 weeks to 2 months after the operation. Some men reported that they could not achieve orgasm until 4 to 10 months after surgery, and one man noticed partial return of penile stiffness at the moment of orgasm 18 months post-operatively.

Thirty-four men were able to give reliable information about the occurrence of nocturnal erotic dreams with orgasm. Pre-operatively, 12 men had had erotic dreams, but one of them was sexually inactive before as well as after the operation, from which time on he had no such dreams. Six of the 8 men who were sexually active post-operatively and one of the 3 men who became inactive after cystectomy continued to have erotic dreams with sensation of orgasm.

Post-operatively, 10 men (mean age 55 years; median age 58; range 24 to 68) had unchanged libido, while 27 (mean age 64 years; median age 64; range 50 to 73) considered it to be somewhat weakened. The difference in age between the 2 groups was statistically significant ($P<0.05$) (Wilcoxon's Test). The man who had resection of the prostate considered his libido to be unchanged.

After cystectomy, 6 of the 17 patients (35%) who had been given pre-operative radiotherapy were sexually inactive compared with 5 of the 21 men who had not been treated (23%). Two patients who were unable to obtain penile erection post-operatively noticed loss of sexual ability during pre-operative radiotherapy.

Electromyographic Registration

The effect of various degrees of extensive surgery in combination with cystectomy was studied electromyographically. The myoelectrical activity of the striated urethral sphincter, the bulbocavernosus muscle, and the levator ani muscle were recorded in 8 patients after cystectomy: prostatectomy and vesiculectomy had been performed in 6, prostatectomy, vesiculectomy and urethrectomy in 1, and prostatic resection and vesiculectomy in 1 man.

Post-operatively, 3 men had not achieved orgasm. During the examination they were not

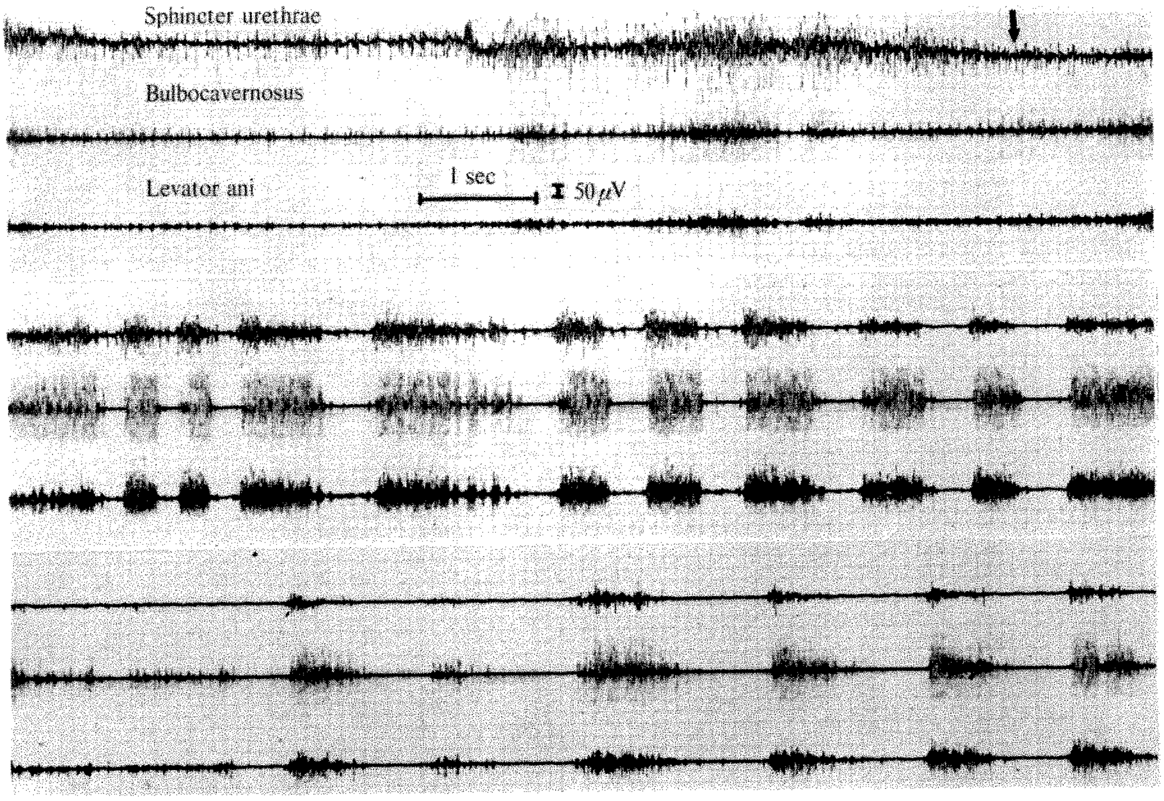

Fig. 1 Continuous EMG-registration from the striated urethral sphincter, the bulbocavernosus muscle, and the levator ani muscle during orgasm of a man treated by cystectomy, prostatectomy, vesiculectomy and urethrectomy. The small arrow indicates the moment of initial sensation of orgasm. The EMG-pattern is normal with respect to duration of muscular contractions and duration of intervals between contractions.

able to obtain erection or orgasm following masturbation, and no increase in rhythmic activity was traced in the muscles during masturbation. Five patients had experienced orgasm post-operatively; 2 of them could not masturbate to orgasm during the examination; no increase in rhythmic activity was recorded. The remaining 3 obtained orgasm; one of them had had total urethrectomy, and one prostatic resection. Figure 1 illustrates the appearance of the EMG-activity pattern during orgasm from the patient subjected to urethrectomy. The amplitude of the activity corresponding to the striated voluntary urethral sphincter was somewhat decreased compared with that of the bulbocavernosus muscle. This might be caused by post-operative changes or dislocation of the electrode during orgasm. No difference in amplitude with respect to the EMG-activity from the urethral sphincter and the bulbocavernosus muscle could be registered before orgasm (the small arrow indicates the moment of initial sensation of orgasm). The EMG-activity patterns of the striated urethral sphincter, the bulbocavernosus muscle, and the levator ani did not diverge from those of normal subjects given by Petersén and Stener (1970) as regards the duration values of EMG-activity on contraction and duration of intervals subsequent to muscular contraction in connection with ejaculation.

Figures 2a and b illustrate the electromyographic patterns during orgasm of the patient treated by cystectomy and prostatectomy. Normal values as regards the duration of EMG-activity on contraction and duration of interval (electrical silence) subsequent to contraction were registered. An enlargement of the curves (Fig. 2b) shows that the activity of the urethral sphincter started somewhat earlier than that of the bulbocavernosus muscle (cf. Kollberg *et al.*, 1962).

Electromyographic registration from the striated external urethral sphincter, the bulbocavernosus muscle, and the levator ani muscle of the man on whom prostatic resection had been performed showed a pattern of impulse during orgasm

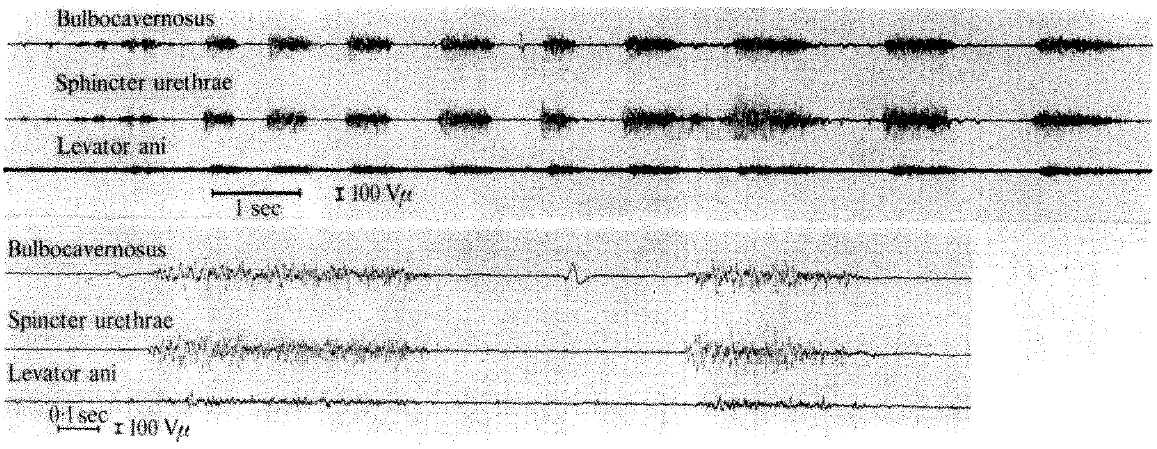

Fig. 2 (a) EMG-registration during orgasm from a man treated by cystectomy, prostatectomy and vesiculectomy. (b) Gives the EMG-activity at a high speed. The clonic contractions of the striated urethral sphincter start somewhat earlier than in the bulbocavernosus muscle.

identical with that of non-operated normal subjects.

Discussion

The reliability of information supplied in sexual matters is difficult to evaluate. If, in this material, the report of the patient was doubted, the sexual partner was interviewed. Retention of the ability to achieve erection and to perform intercourse could thereby be verified by 2 partners. In one case this ability was denied by a woman and her husband was excluded from the study.

Elderly men were very difficult to interview with respect to their sexual activity and sometimes the physician was not successful until he had met them on several occasions during the follow-up. Some of them denied sexual activity at the first interview. At later discussions, however, they reconsidered and admitted masturbation. This reticence must be remembered when evaluating sexual activity in elderly subjects. Older patients subjected to cystectomy, despite having their former sexual partners, frequently attempted to achieve orgasm by masturbating alone. Young men more frequently tried to achieve orgasm by mutual masturbation. Ten men lost their libido and erection ability after the operation. This could possibly be explained by loss of the female partner in 2 cases. In the remaining 8 cases, the loss of sexual ability might have been influenced by their age (mean age 64 years) and/or disturbances of sexual habits. Kinsey *et al.* (1948), Finkle and Saunders (1960) and Newman and Nichols (1960) stated that the sexual drive decreases in higher age groups. If a major urological operation is performed, the psychological trauma might completely extinguish the small and declining sexual power.

Some men in this study noticed a gradual improvement in their sexual ability during the first 18 months after surgery, which confirms the observation of Stahlgren and Ferguson (1958) of increasing sexual ability during the first post-operative year after excision of the rectum. Glass and Spratt (1968) reported that 24 of 117 patients (13%) who had undergone excision of the rectum had urinary retention at least one week after operation. Fourteen (58%) of them reported a regression of micturition difficulties during the following 3 months. The return of function after surgery may be explained by diminishing oedema around nerves and vessels and by revascularisation and/or regeneration of nerves. To minimise the influence of these factors on the evaluation of post-operative sequelae, all patients in this study were interviewed more than 12 months after cystectomy.

Intact vascular supply of the corpora cavernosa of the penis and preserved parasympathetic innervation are prerequisites for penile erection. The most plausible explanation for loss of the ability to obtain erection after major pelvic surgery, *e.g.* retropubic or perineal prostatectomy, is damage to nervous pathways (Ward, 1936-37; Finkle *et al.*, 1959; Finkle and Saunders, 1960; Dlin *et al.*, 1969). This has also been considered to be the main cause of lost erection ability after abdominoperineal excision of the rectum. Damage to the pelvic nerves can occur, particularly during the pre-sacral dissection. In the present series only 3 patients preserved their ability to obtain erection post-operatively, which indicates the difficulty in avoiding damage to the pelvic nerves and the penile vessels during cystectomy, prostatectomy and vesiculectomy. It is not possible, on the basis of this study, to evaluate the relative importance of nervous and vascular damage. Probably, however, nerves as well as vessels are damaged. The loss of erection ability during pre-operative radiotherapy noticed by 2 men might have been caused by oedema around the nerves and vessels with subsequent rigidity of the tissue. However, general tiredness, advanced age and psychological factors, as well as local influence from the tumour, might also have been of importance.

In normal, non-operated subjects, contractions of the striated pelvic floor and urethral muscles were registered (Kollberg *et al.*, 1962) simultaneously with the experience of orgasm. Intact pudendal nerves are a prerequisite for contraction ability of these muscles. Thus an intact bulbocavernosus reflex is expected in men who can experience orgasm. In our study 7 men were unable to achieve orgasm. Some of them, however, had an intact bulbocavernosus reflex. This shows that the loss of orgasm cannot be ascribed to damage to the pudendal nerves only. It might be possible that the experience of orgasm is mediated through specific fibres in the pudendal nerves. These fibres are selectively damaged and the preserved fibres mediate the reflex.

By means of electromyographic registration, impulse patterns similar to those found in normal subjects during orgasm were recorded in this study. Kinsey *et al.* (1948) and Romanus (1948) considered that orgasm could occur without ejaculation and without flow in the urethra. The present investigation supports their opinion. An unchanged orgasm and a normal EMG-pattern in a man who had been treated by urethrectomy shows that neither the smooth muscles of the urethra nor the *corpus spongiosum urethrae* are essential for the experience of orgasm.

Two men reported the occurrence of morning erections. In our opinion this supports the theory that spontaneous erection may be released from CNS activity during sleep and not from distension of the urinary bladder.

The occurrence of erotic dreams in 6 out of 8 men who post-operatively were sexually active and the loss of dreams in 2 of the 3 men who were inactive support the theory of Money and Hirsch (1965) that retention of the CNS pathway is necessary to retain this ability to dream.

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A Trial of Bleomycin versus Adriamycin in Advanced Carcinoma of the Bladder

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Summary—Thirty-seven patients were studied in a controlled clinical trial to assess the value of Adriamycin and Bleomycin in the treatment of advanced carcinoma of the bladder. The previously reported high response rates for both drugs were not observed in this trial.

Administration of Bleomycin was accompanied by a toxicity rate so high that treatment had to be abandoned. Neither Adriamycin nor Bleomycin, therefore, used as single agents, have a role in the chemotherapy of advanced bladder cancer.

Other agents should be investigated and assessed by controlled clinical trials that are disease-orientated rather than drug-orientated.

The management of the patient with recurrent local or disseminated bladder cancer presents a difficult clinical problem. Salvage surgery for recurrent local disease is possible in a very small number of cases (Wallace and Bloom, 1976) but in a large number of such cases, or those with disseminated disease, surgery or radiotherapy is of no value. Until recently the role of chemotherapy in this situation has remained ill-defined as chemotherapeutic agents have not been intensively studied.

Carter and Wasserman (1975), in a review of chemotherapy for bladder cancer, could find reports of only 11 chemotherapeutic agents that had been used in bladder cancer; with 8 of these agents the number of patients studied was 10 or less as these were usually included in drug-orientated series. Only 3 drugs, therefore, had received a possible significant evaluation and each had shown some evidence of activity. Of these, Adriamycin was reported as giving a response rate of up to 35% (Middleman *et al.*, 1971; Bonadonna *et al.*, 1972; O'Bryan *et al.*, 1973). In other studies a response rate of up to 33% was observed in patients treated with Bleomycin (Völter and Staehler, 1971; EORTC, 1974; Pavone-Macaluso and EORTC, 1976).

In view of these reports, a controlled clinical trial to compare the regression rate and morbidity of Adriamycin and Bleomycin in advanced cancer was instituted.

Patients and Methods

Patients were entered from each member of the London and Oxford cooperative group and treatment selection was randomised. Thirty-seven patients were entered into the trial. Three patients drawn for the trial did not receive the drug and one was lost to follow-up, so that information is available on 33.

Eleven patients received Adriamycin only, 13 Bleomycin only, and 10 received both drugs. Patients who received only one agent did not receive the other either because progressive disease caused severe debility or the patient died. No patient received an extended course because of a noted response. Cases were eligible for entry when the following criteria were fulfilled:

1. There was histological proof of urothelial carcinoma of the bladder.
2. The disease was (a) disseminated or (b) recurrent at least 6 months after radical radiotherapy.
3. There was no second primary tumour.
4. No previous cytotoxic chemotherapy had been given.
5. The patient was medically fit to undergo the required investigations and to receive either drug regime. Patients with cardiac impairment, abnormal liver function tests or renal failure were not included.

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The following treatment schedules were used: Adriamycin 25 mg/m^2 intravenously every 3 weeks or Bleomycin 5 mg/m^2 intramuscularly twice weekly.

Reassessment was made at 12 weeks. If the patient had responded then the following regimes were used: Adriamycin 25 mg/m^2 intravenously every 4 weeks or Bleomycin 5 mg/m^2 intramuscularly every week, to a total dose of Adriamycin 500 mg/m^2 or Bleomycin 300 mg/m^2.

For those patients who did not respond after the initial course of 12 weeks the regime was changed from Adriamycin to Bleomycin or vice versa.

Pre-Treatment Investigations

Pre-treatment investigations included full blood count, renal and liver function tests, urine culture and cytology, radiology of the chest, urinary tract and lymphography prior to staging under general anaesthesia.

All investigations were repeated after 12 weeks.

Criteria of Response

Only objective responses were considered and were divided into 2 categories:

(1) *Complete:* complete regression of tumour lasting at least 6 months.

(2) *Partial:* objective reduction in size of metastatic deposits as seen radiologically and/or downstaging of bladder tumour assessed under general anaesthesia.

Toxicity

Toxic side effects for each drug were noted. For patients receiving Adriamycin, when the white cell count fell to less than 2000/μl or platelet count to less than 90,000/μl, the dose was postponed. Patients receiving Bleomycin were watched for increased skin pigmentation, skin and mucous membrane ulceration and lung symptoms. If the latter developed, then the drug was discontinued.

Results

An analysis of the overall results is shown in the table. No complete responses were seen in either group. Two partial responses, in each case a reduction in node volume as observed by decrease in lymphographic size on repeated radiographs, were observed in patients receiving Adriamycin. This gives a response rate for the drug of 9.5%. Two partial responses, each consisting of an improvement in the local bladder tumour, were observed in patients receiving Bleomycin, giving an overall response rate of 8.7%.

Toxic effects severe enough for the course of treatment to be abandoned were not observed in patients receiving Adriamycin. This is in contrast to the serious side effects, both pulmonary and affecting the mucous membrane, noted in patients receiving Bleomycin. These effects were so severe in 26% of patients that the course had to be abandoned. In each case the effects were noted at very low total doses—much lower than the 300 mg/m^2 maximum dose laid down by the trial protocol.

Discussion

Evaluation of chemotherapeutic agents in the management of bladder cancer has been based mainly on drug-orientated studies rather than controlled clinical trials for stages of a disease. Recently, the trend has been towards multiple agent regimes rather than assessment of the effectiveness of single agents.

This paper demonstrates the need for the controlled clinical trial to assess the exact value of the drug used as a single agent.

Adriamycin was initially reported as having a response rate of about 35% (Middleman *et al.*, 1971; Bonadonna *et al.*, 1972; O'Bryan *et al.*, 1973), but later trials observed response rates of 14% (Yagoda *et al.*, 1977), 10% (Merrin *et al.*, 1975), and even nil (Tan *et al.*, 1973). The finding in this trial of a 9.5% response rate is, therefore,

Table

	Drug	
	Adriamycin	*Bleomycin*
Total number	21	23
Full course	14	7
Part course		
Reason:		
Death	7	10
Toxicity	-	6
Responses		
Complete	0	0
Partial	2*	2†
Response rate	9.5%	8.7%
Toxicity	0	6/23 = 26%

* Both decrease in nodal volume.
† Both decrease in bladder tumour.

in support of these lower rates. The recorded response rate of 9.5% may itself, however, be too high. Following any lymphogram there is a known spontaneous reduction in size of nodes and the partial responses noted may in fact be within the range of normal.

The dose schedules commonly used in other series were intermittent—either 20 to 30 mg/m^2 per day of Adriamycin for 3 days, 20 to 35 mg/m^2 once every 7 days, or 60 to 105 mg/m^2 every 21 days (Middleman *et al.*, 1971; Frei *et al.*, 1972; Benjamin *et al.*, 1973; Hahn *et al.*, 1973; O'Bryan *et al.*, 1973).

In our trial the dosage was lower because it was considered that a potential cardiotoxic drug (Wang *et al.*, 1971; Benjamin *et al.*, 1972) should not be given to an older group of patients even though cardiac assessment was normal. No cardiotoxic effects were observed with Adriamycin in the dosage used and the response rate was comparable with that of the other higher dose series (O'Bryan *et al.*, 1973; Tan *et al.*, 1973; Yagoda *et al.*, 1977). Thus the low response rate is not a reflection of the low dose but of the efficacy of the drug in this disease.

Previous reports have suggested that Bleomycin had potential activity and a response rate of up to 33.3% has been reported (Middleman *et al.*, 1971; Bonadonna *et al.*, 1972; O'Bryan *et al.*, 1973). In this and other series there were no reports of the toxic effects that were seen in our study. The drug dosage was low because concern had been expressed, as with Adriamycin, on possible risks to older patients; despite this, 26% had toxic effects severe enough for treatment to be abandoned. This complication is unacceptably high for any treatment. The exact reason for the high incidence remains unexplained.

The overall response rates for the 2 drugs is about the same but the trial has demonstrated a very high morbidity in patients treated with Bleomycin. These rates are lower than those reported for other agents, *e.g.* Methotrexate (Turner *et al.*, 1977), Cyclophosphamide (Carter and Wasserman, 1975) and Cis-platinum (Yagoda *et al.*, 1976). Again, all reports are of drug-orientated series rather than the controlled clinical trials to which these agents must now be subjected.

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Gelatin Foam and Isobutyl-2-Cyanoacrylate in the Treatment of Life-Threatening Bladder Haemorrhage by Selective Transcatheter Embolisation of the Internal Iliac Arteries

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Summary—Three patients with severe haemorrhage from inoperable bladder cancer were treated by selective transcatheter embolisation of both internal iliac arteries. The technical details, results and a rare complication are described. Both gelatin foam and isobutyl-2-cyanoacrylate (IBC)* are suitable embolic materials, but we prefer IBC when possible in patients with tumour.

Intractable bleeding from advanced carcinoma of the bladder is well known to the urologist and represents a major therapeutic problem. The blood loss is often severe and the general condition of the patient poor. Recently, cases have been successfully treated by angiographic embolisation of the internal iliac arteries (Küss *et al.*, 1975; Mitchell *et al.*, 1976; Schuhrke and Barr, 1976; Higgins *et al.*, 1977).

We report our experience with such a method and consider the technique and the choice of embolic material. A very rare, previously undescribed complication is also discussed.

Case Reports

Case 1

C.A., a 65-year-old man with inoperable bladder carcinoma, was admitted with recurrent episodes of severe haematuria. Biopsy of enlarged inguinal lymph nodes revealed metastatic involvement by transitional cell carcinoma. The left leg was oedematous and painful. Skin metastases were present. The stage of the tumour was T3N2M1. Haematuria increased and caused clot retention. An angiographic study was made (Fig. 1a) and the left internal iliac artery, selectively catheterised through a transaxillary approach, was embolised with finely fragmented gelatin foam (Fig. 1b). The gluteal artery was preserved. The urine became clear and the oedema of the leg improved.

A recurrence of haematuria 15 days later prompted us to make another angiographic study which demonstrated persistence of the occlusion of the anterior trunk of the left internal iliac artery (Fig. 1c) but showed revascularisation of the tumour from the opposite side and from branches of the left gluteal artery (Fig. 1d). Through a transaxillary approach the right internal artery was catheterised and embolised with gelatin foam at the level of the gluteal artery. Embolisation of the left internal iliac artery was completed with occlusion of the gluteal artery. Haematuria ceased and the urine remained clear during the following 2 months in which the patient was in hospital. Severe gluteal and upper thigh pain developed immediately after embolisation but resolved spontaneously after a few days. The patient underwent a cycle of antiblastic therapy and was discharged 60 days after embolisation. He died from metastases 4 months later without bleeding again.

Case 2

I.E., an 84-year-old woman, had advanced bladder malignancy (T3NXMO). Her poor general condition and advanced age contraindicated surgical intervention. Brisk haemorrhage from the bladder caused severe anaemia and her haematocrit fell to 18%. The right internal artery was selectively catheterised via a contralateral transfemoral approach (Fig. 2a) and embolised with 1 ml IBC + 1 ml Lipiodol. A radio-opaque cast of the embolised arterial tree is clearly seen in a straight X-ray of the pelvis 7 days after embolisation (Fig. 2b). Bleeding stopped immediately after embolisation but recurred later. Angiography was again carried out and the left internal iliac artery selectively catheterised by a contralateral transfemoral approach and embolised

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* Supplied by Ethicon Ltd. Not authorised for use in humans in Great Britain.

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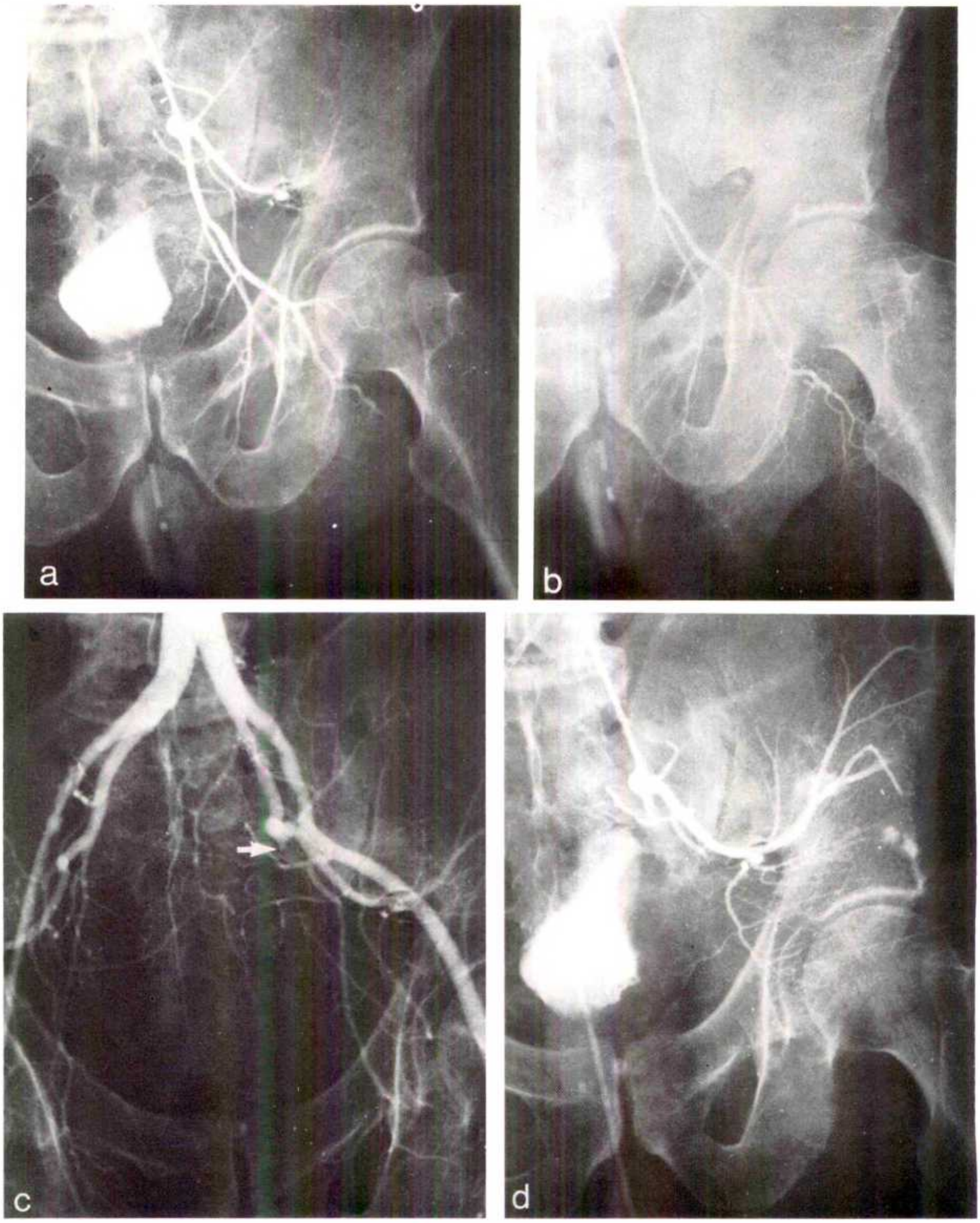

Fig. 1 Case 1: (a) Selective catheterisation of the left internal iliac artery through a transaxillary approach. (b) The catheter has been advanced into the anterior division of the internal iliac artery beyond the origin of the gluteal artery. (c) Aortography 15 days after embolisation: the anterior trunk of the internal iliac artery appears completely occluded. (d) Selective arteriography of the embolised left internal iliac artery: the anterior division is occluded, but several small branches of the gluteal artery vascularise the tumour.

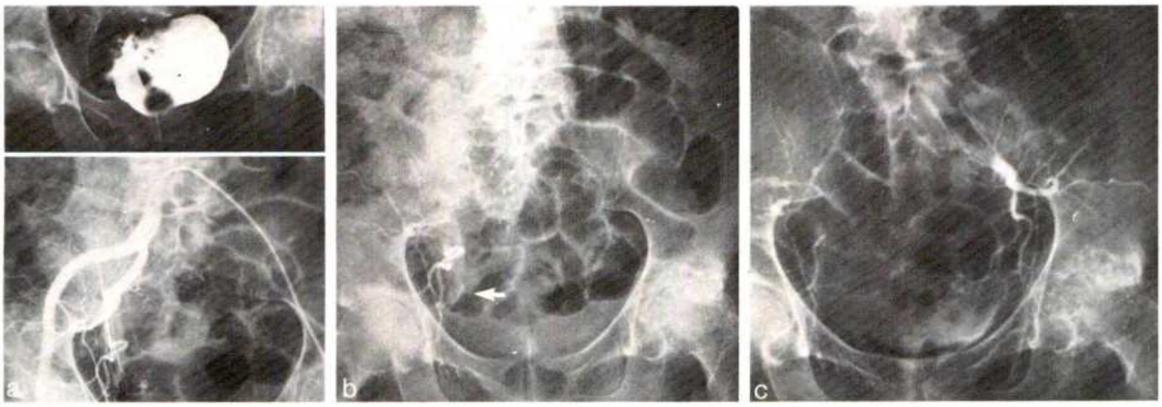

Fig. 2 Case 2: (a) Right iliac arteriography through a transfemoral contralateral approach. (b) Plain X-ray of the pelvis 7 days after embolisation. The embolised arterial tree can clearly be seen owing to the radio-opacity of Lipiodol. (c) Plain X-ray of the pelvis 2 days after left internal iliac embolisation with IBC-Lipiodol.

with IBC and Lipiodol (Fig. 2c). The urine became clear and the haematocrit rapidly increased to 35%. Transient gluteal pain quickly resolved and the patient was discharged 20 days after embolisation, free of haematuria and with normal bladder function. She remained free of bleeding for 8 months, when she died from a cerebrovascular accident.

Case 3

D.A.P., a very obese 52-year-old man, was admitted with extremely severe bladder haemorrhage and clot retention. IVP revealed a large filling defect in the bladder due to a transitional cell carcinoma (T2NXMO). Haematocrit was 25% and continued to fall despite blood replacement. A one-stage bilateral embolisation was decided upon and selective catheterisation of both internal iliac arteries via ipsilateral transfemoral approaches was carried out (Fig. 3a). The right internal iliac artery was embolised with IBC and Lipiodol; after a first injection of IBC and Lipiodol the left internal iliac artery required a complementary injection of gelatin foam (Fig. 3b).

Immediately after embolisation the urine became clear. Severe gluteal and upper thigh pain required anaesthetic spinal block with 10 ml 1% lidocaine. Two days later the patient complained of motor deficiency on the left side and rapidly developed a complete

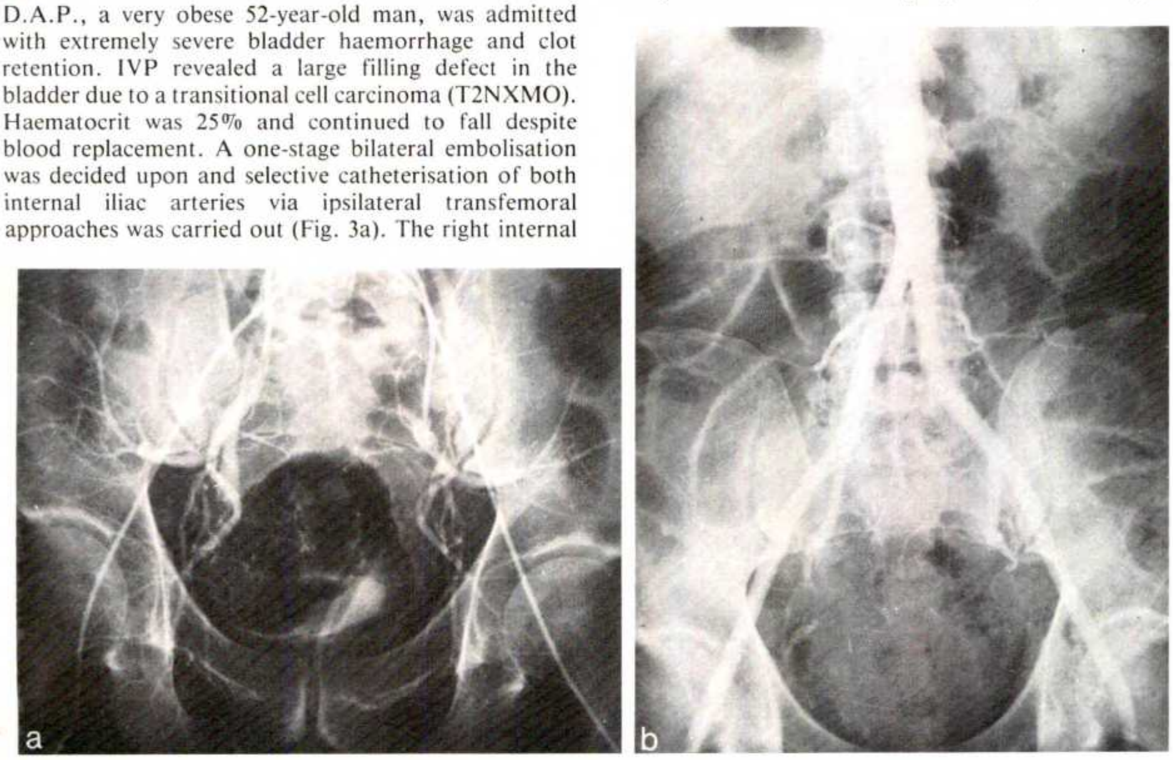

Fig. 3 Case 3: (a) Selective catheterisation of the anterior division of each internal iliac artery through an ipsilateral transfemoral approach. (b) Aortography shows that internal iliac bilateral occlusion persists.

paralysis of the left leg Neurological examination revealed a Brown-Séquard-like syndrome, probably due to spinal cord damage at the level of D10. Transient incontinence was also observed after the removal of the urethral catheter. Three months later the patient remained free of haematuria and his paralysis had improved to the extent that he could walk with the aid of a support. The urine remained clear and IVP revealed a remarkable decrease in the size of the neoplasm. The right ureter, which was markedly dilated before embolisation, was completely normal. A transurethral resection was therefore carried out and the patient was discharged 4 months after embolisation.

Discussion

Pelvic transcatheter embolisation is useful in cases of severe haematuria from inoperable bladder cancer. The alternatives are surgical ligation of internal iliac arteries, Helmstein's hydrostatic procedure or bladder irrigation with formalin, none of which have had good results. The technical difficulties, the possibility of revascularisation, the fear of bladder necrosis and of distal embolism have hindered the clinical application of bilateral internal iliac embolisation.

Selective catheterisation of the internal iliac arteries is possible in nearly all patients by an experienced angiographer and can be done by the transaxillary or by the ipsilateral or contralateral femoral approach.

Revascularisation of an embolised arterial tree has been described when clots were used as embolic material, and also when gelatin foam was used. Although revascularisation with gelatin foam was not seen, we preferred to use a new embolic material—isobutyl-2-cyanoacrylate (Bucrylate, Ethicon). Previously used in surgery as a tissue adhesive, its use as an embolic material is relatively recent, but already several reports have been published (Carmignani *et al.*, 1977; Giuliani *et al.*, 1977a). Radio-opaque tantalium powder has been used to make IBC (Dotter *et al.*, 1975). Since this material was not available to us, we mixed IBC with a non-ionic lipid substance (lipiodol) with good results (Giuliani *et al.*, 1977b). Pelvic embolisation for bladder cancer should always be bilateral because the vessels from the contralateral side caused recurrence of bleeding in all of our cases.

Provided that the technique is correct the only complication is severe pain in the buttocks and the upper thighs, which resolves in a few days and may be prevented by preserving the gluteal artery. In none of our cases did the bladder necrose or its function change, other than transiently. In one patient (Case No. 3) we observed a very rare complication, the aetiology of which we are unable to explain. Spinal lesions have occasionally been described in renal embolisation because emboli spill into the great spinal artery of Adamkievicz, but this seems impossible during embolisation of an internal iliac artery. In addition, a vascular injury should manifest itself immediately after the accident, whereas the paralysis appeared 2 days later in our case. It is concluded that selective transcatheter embolisation of the internal iliac arteries is a safe and effective procedure which can be successfully used in every case of intractable haematuria from inoperable bladder carcinoma and which does not prejudice further procedures.

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The Assessment of Prostatic Obstruction from Urodynamic Measurements and from Residual Urine

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Summary—One hundred and seventeen males over the age of 55 were investigated for possible prostatic obstruction. About half of the cases in this series could have been objectively classified as unobstructed or obstructed from the maximum flow rate alone.

In about two-thirds of the cases obstruction could be satisfactorily assessed from the maximum flow rate together with the detrusor pressure at maximum flow. It was not helpful to combine these 2 measurements into a single urethral resistance factor.

In the remaining one-third of the cases, obstruction could be objectively assessed only from a plot of detrusor pressure against flow rate throughout micturition. In many of these cases both the pressure and the flow rate were low and the main peculiarity was that the contractile power of the bladder was weak.

Residual urine is a sign of an abnormality of bladder function rather than the direct result of urethral obstruction.

Measurements of bladder pressure and flow rate during micturition make it possible, in principle, to distinguish objectively between an obstructed and unobstructed urethra. It is not clear, however, what criteria should be used for the most reliable assessment. Often the maximum flow rate and either the intravesical or the detrusor pressure at that flow rate are used as criteria; sometimes these are combined into a single urethral resistance factor (Smith, 1968). It has been suggested that a plot of detrusor pressure against flow rate throughout micturition should be a useful way of detecting obstruction (Griffiths, 1973, 1974; Bates *et al.*, 1975).

In this paper it is first shown that such pressure/flow plots are a sensitive and reproducible test of prostatic obstruction, both before and after prostatectomy. A series of patients is then classified according to the pressure/flow plots and it is argued (i) that the majority can in fact be objectively classified as clearly obstructed or unobstructed by simpler methods, but that there is a substantial borderline group in which obstruction can be assessed only by the pressure/flow plot; (ii) that in the borderline group there are both unobstructed and obstructed patients whose main urodynamic peculiarity is a reduced contractile power of the bladder; (iii) that residual urine is a sign of an abnormality of bladder function and not the direct, mechanical result of urethral obstruction.

Patients and Methods

The series consisted of 117 males of 55 years and over who, apart from a few exclusions for technical reasons, were taken without selection from those in this age group referred to the Unit for investigation of possible prostatic obstruction. Fifteen of these patients were examined again about 3 months after prostatectomy (either retropubic or transurethral). In 8 of the patients 2 pressure/flow plots were obtained before any operation, either (a) on the same occasion or (b) on 2 occasions separated by an interval of about 6 months, during which they received either a placebo or a drug that proved to have no detectable urodynamic effect (Abrams, 1977a).

After measurement of the urethral closure pressure profile and filling cystometry, the patient micturated, seated and with a transurethral epidural catheter (Portex 100/380/300) in place, while intravesical and rectal pressures and the

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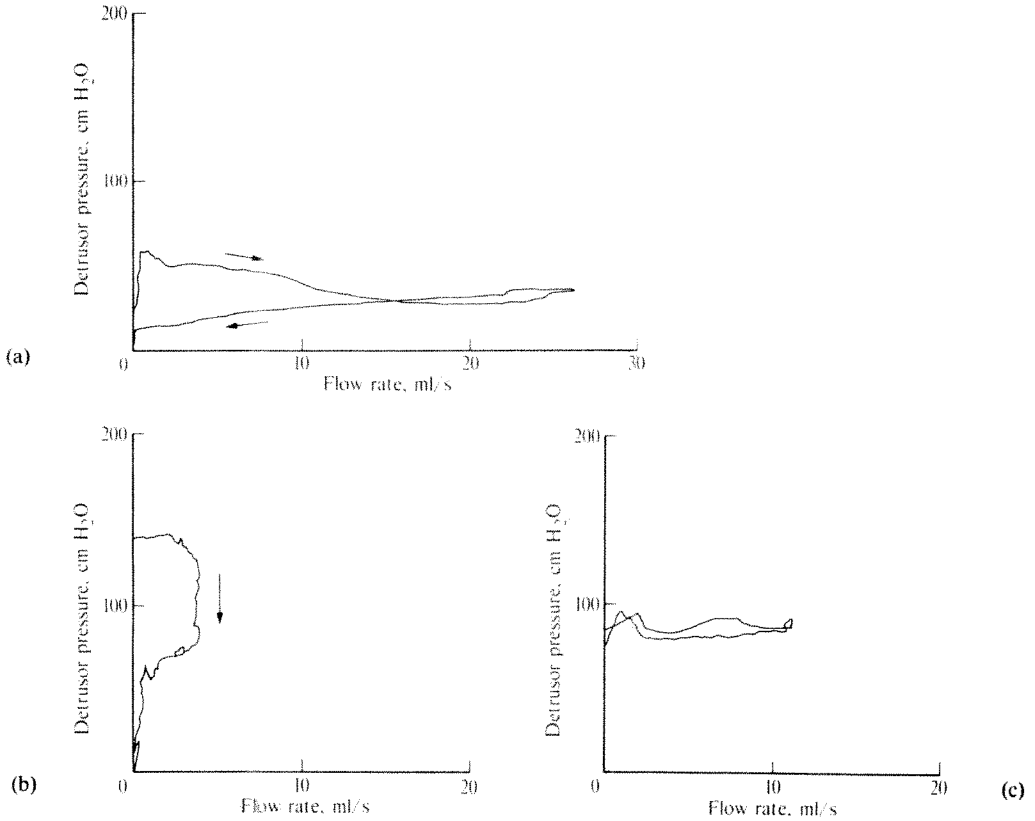

Fig. 1 Pressure/flow plots for micturition of 3 different unoperated patients: (a) unobstructed pattern A: characteristics are that plot is nearly horizontal (*i.e.* mean slope is small) and pressure at end of voiding is low; (b) obstructed pattern B: main characteristic is that plot is not horizontal, so that mean slope (after fast initial rise of flow rate) is large; also plot is often curved, as here; (c) obstructed pattern C: plot is nearly horizontal but pressure at end of voiding is high. 1 cm H_2O is approximately 100 Pa, the S.I. unit of pressure.

volume voided were measured (Siemens-Elema EMT 34 and 435 transducers). Detrusor pressure (=intravesical pressure—rectal pressure) and volume flow rate were calculated electronically. All 5 variables were recorded on a chart recorder (Siemens-Elema M81) and on tape (Ampex PR 500 recorder). Residual urine was estimated by subtracting the voided volume from the volume previously introduced into the empty bladder, or was measured by catheterisation.

The magnetic tapes were played back to an x-y recorder (Bryans 26000/A4), with some smoothing to reduce noise artefacts, so that detrusor pressure was plotted against flow rate throughout each micturition as illustrated in Figure 1. No account was taken of the unavoidable time lag of about 1 s in the measurement of the flow rate.

Urethral obstruction was also assessed clinically by one of the authors (P.H.A.), prior to and independently of the work described here. The criteria and further details of the methods used have been described elsewhere (Abrams, 1976, 1977b; Abrams *et al.*, 1977).

Results

Illustrative Results

Figure 1 shows 3 representative pressure/flow plots, which are respectively (a) unobstructed, pattern A, and (b) and (c), obstructed patterns B and C. Pattern B is the commoner obstructed pattern. Pattern C is similar to A but is displaced to much higher pressures; it is uncommon. The criteria for classification are discussed below.

Figures 2i and ii show how a severely obstructed pattern is changed into an unobstructed pattern A by successful prostatectomy.

Figures 3a and b show 2 pre-operative plots from the same patient, separated by 6 months without intervening surgery. The pattern is an

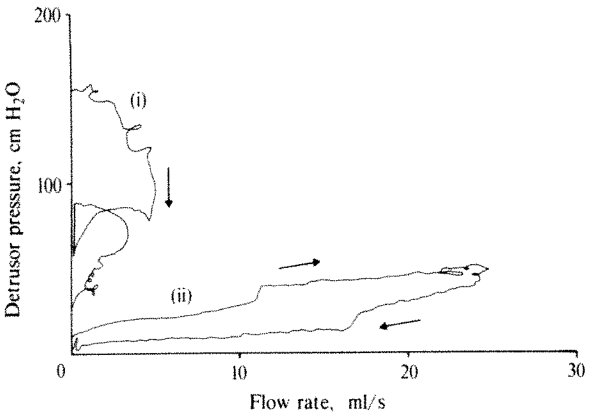

Fig. 2 Pressure/flow plots for 2 micturitions of one patient. (i) before prostatectomy: obstructed, pattern B; (ii) after prostatectomy (TUR): unobstructed, pattern A.

obstructed one (B) on both occasions, although there are small quantitative changes.

Classification

Previous experience (Griffiths, 1973; Bates *et al.*, 1975) suggests that, in unobstructed cases, the mean slope of the pressure/flow plot (after the fast initial rise in flow rate) is less than 2 cm H_2O/ml s^{-1} and the detrusor pressure as flow ceases at the end of voiding is 40 cm H_2O or less. Plots satisfying these 2 criteria have been classified as unobstructed, pattern A. Plots with mean slope greater than 2 cm H_2O/ml s^{-1} have been classified as obstructed, pattern B, and those with mean slope less than 2 cm H_2O/ml s^{-1} but detrusor pressure at the end of voiding greater than 40 cm H_2O have been classified as obstructed, pattern C. Plots with pattern B are often curved (Figs. 1-3), so that the mean slope can only be roughly estimated. However, this leads to very little ambiguity since, in fact, such curvature is helpful in classifying the pattern as obstructed, type B.

Of the 117 unoperated patients, 21 showed an unobstructed pattern A and 91 showed obstructed patterns; 3 could not be unambiguously classified; 85 of the 91 obstructed patterns were of type B and only 6 of type C.

Of the 15 patients examined before and after prostatectomy, 14 had plots of pattern B and 1 of pattern C before operation. After operation 13 showed the unobstructed pattern A and 2 showed evidence of slight residual obstruction, pattern B.

Comparison with Clinical Assessment

These pre-operative and post-operative results are compared graphically in Figure 4 with the clinical assessment, which is based on symptoms, signs and urodynamic criteria different from those described here (Abrams, 1976, 1977b; Abrams *et al.*, 1977). For each patient's micturition (selected arbitrarily, if there was more than one similar micturition) a point is plotted showing the maximum flow rate and the detrusor pressure at maximum flow. The symbols show whether the 2 assessments agree that there is obstruction (triangles) or no obstruction (circles), or whether there is doubt in either assessment or disagreement between them (squares). As one would expect, there is agreement in virtually all the clear-cut cases (high pressure with low flow rate or low pressure with high flow rate), and nearly all the doubtful cases fall in a borderline region of moderate to low detrusor pressures and flow rates.

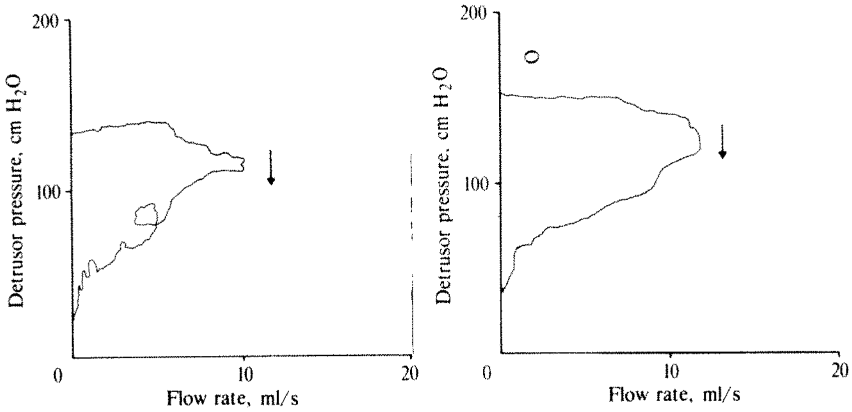

Fig. 3 Pressure/flow plots for 2 micturitions of one patient. (a) before treatment; (b) 6 months later, with no intervening surgery. Both plots show the obstructed pattern B.

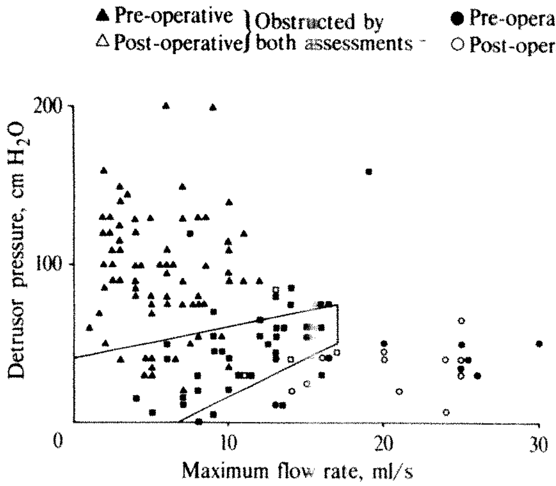

Fig. 4 Comparison between the assessments of obstruction by 2 independent means, namely clinically and from the pressure/flow plots, for pre-operative micturitions of 102 males and for pre-operative and post-operative micturitions of 15 males. Each micturition is represented by a point showing the maximum flow.

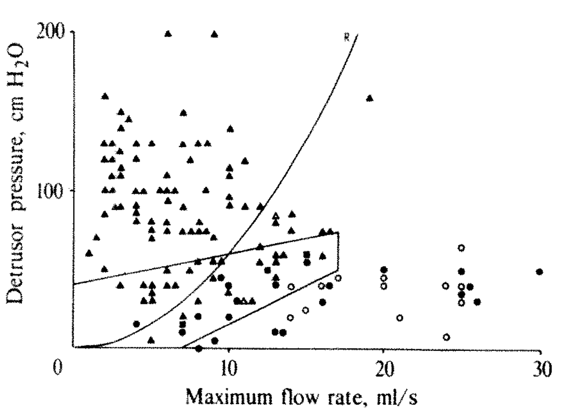

Fig. 5 The result of assessing obstruction by the pressure/flow plots alone, for the same micturitions as in Figure 4. The region enclosed by straight lines is a borderline region where obstructed and unobstructed cases are, or could in principle be, intermingled. All points falling on the curve labelled R have a urethral resistance factor (p_{det}/Q_{max}^2) of 0.6 cm $H_2O/ml^2\ s^{-2}$.

When the results of the urodynamic assessment of the pressure/flow plots are plotted without reference to the clinical assessment (Fig. 5), the number of "doubtful" cases is much reduced. A borderline region is still apparent, however, as an area on the graph where obstructed and unobstructed cases are mingled. The borderline region outlined in Figure 5 includes both this area and also, on the higher-pressure side, an area where mingling could in principle occur, according to the criteria used to classify the pressure/flow plots.

Discussion

Objective Assessment of Obstruction by Simple Criteria

Figures 4 and 5 show that many cases can be assessed reliably from a simple measurement of maximum flow rate (Q_{max}) alone. For example, if all cases with $Q_{max} = 20$ ml/s or more are taken as unobstructed, and all with $Q_{max} = 6$ ml/s or less are taken as obstructed, 49% of the unoperated results and 53% of the post-operative results can be classified. This classification agrees with that deduced from the pressure/flow plot in every case except one (98%).

If the detrusor pressure p_{det} at maximum flow is taken into account also, all the cases which fall outside the borderline region outlined in Figure 5 can be classified; that is, about two-thirds of the unoperated results and nearly all of the post-operative results. This still leaves a substantial proportion of cases unclassified, however, and these can only be assessed objectively from the complete pressure/flow plot.

It is common to combine Q_{max} and p_{det} into a single urethral resistance factor, e.g. p_{det}/Q_{max}^2 (Smith, 1968). In Figure 5, a curve corresponding to a constant urethral resistance factor of 0.6 cm $H_2O/ml^2\ s^{-2}$, calculated according to this formula, is shown. Obviously it separates the clearly obstructed from the clearly unobstructed patient. However, the resistance factor cannot distinguish between cases in the borderline region. Moreover, it fails to show whether a case falls in the borderline region or not, and so confuses clear-cut and doubtful cases. For example, among the cases in Figure 5 with a urethral resistance factor near 0.6 cm $H_2O/ml^2\ s^{-2}$, there are some outside the borderline region which are certainly obstructed and some within the borderline region which are not obstructed, as well as some which are. Resistance factors calculated from other formulae have similar disadvantages. Therefore they are not helpful in practice, just as they are not valid in theory (Griffiths, 1973). It is better to assess obstruction from the maximum flow rate and the detrusor pressure at maximum flow separately, perhaps by plotting them graphically as in Figure 5, in order to see whether they fall in the obstructed, unobstructed or borderline regions.

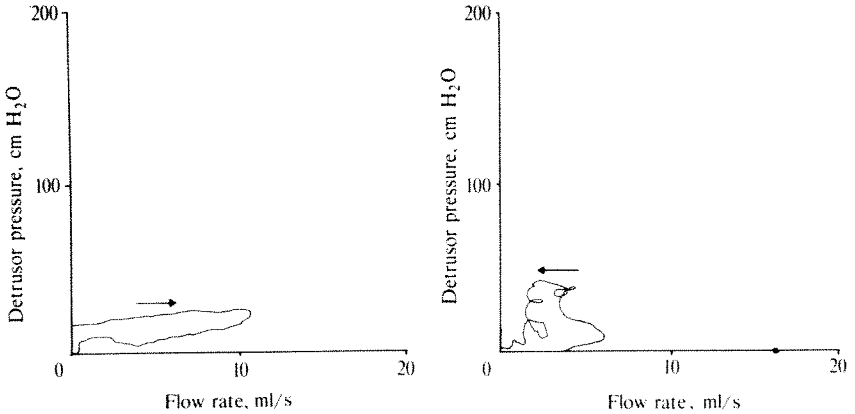

Fig. 6 Pressure/flow plots for 2 different unoperated males in the borderline region of Figure 5. Both have low pressures and low flow rates, yet (a) has the unobstructed pattern A, while (b) has the obstructed pattern B.

Cases in the borderline region can then be looked at more carefully, by means of the pressure/flow plot.

Low-Pressure, Low-Flow Cases in the Borderline Region

Figures 6a and b show the pressure/flow plots of 2 unoperated cases falling in the borderline region of Figure 5. They are not readily distinguishable on the basis of Q_{max} and p_{det} but, as judged from their patterns, Figure 6b is obstructed and Figure 6a is not. In both cases the voided volume was sufficient to ensure that the low flow rate was not unrepresentative, and this is known also from a preliminary flow-rate check before the urodynamic examination. Presumably the low flow rate in Figure 6a is due to a reduced contractile power of the bladder muscle. In Figure 6b the low flow rate again occurs at relatively low pressure, despite the evidence of obstruction, again suggesting a reduced bladder contractile power. A measure of the mechanical power developed by the bladder at maximum flow is $Q_{max} \times p_{det}$. For example, a normal flow rate of 25 ml/s at a normal detrusor pressure of 40 cm H_2O would correspond to a power of 1000 cm H_2O ml/s, *i.e.* 100 mW.

Six of the cases which fell in the borderline region before operation were examined again after operation. Post-operatively all had increased maximum flow rates. The average power at maximum flow was 17 mW pre-operatively, while it rose to 57 mW after operation, an increase of 240%. Individually the changes in power ranged from −20 to +1400%.

Nine cases which before operation were definitely obstructed, not in the borderline region, were examined again post-operatively. All were urodynamically improved by operation as judged from their pressure/flow plots (cf. Fig. 2). For these the average power at maximum flow changed from 70 mW before to 80 mW after operation, an increase of only 14%. Individually the changes ranged from −60 to +170%.

It therefore appears that prostatectomy has a relatively small effect on the bladder power in clearly obstructed cases, but that in the borderline low-pressure, low-flow cases its main effect is, paradoxically, to raise the bladder power to a more normal value.

Residual Urine

The observation of residual urine is commonly taken as a sign of obstruction. Of the 117 unoperated cases examined, 77 (66%) had residual urine of 50 ml or more (mean value used if more than one measurement). The average residual urine was 116 ml. These figures are much higher than those for the normal population (Hinman and Cox, 1967), apparently confirming the association of residual urine with obstruction. However, among the 21 unoperated cases classified urodynamically as unobstructed, 11 (52%) had residual urine of 50 ml or more and the average volume was 74 ml. In this series, therefore, the association with obstruction is rather weak, as was found also by Turner-Warwick *et al.* (1973).

One may therefore ask: is the urethral obstruction the immediate cause of the residual urine? That is, is the detrusor pressure demanded by the obstructed urethra so high that a normally functioning bladder could not empty through it? Or is the cause an abnormality of bladder function, possibly secondary to urethral obstruction? The residual urine is left in the bladder at the end of voiding and therefore, if the high pressure demanded by the urethra is its immediate cause, it is the detrusor pressure at that moment that should be examined. Many obstructed patients have pressure/flow plots of pattern B (Fig. 1b) in which the detrusor pressure at the end of voiding is much lower than that at maximum flow. The pressure and urethral resistance at this moment in fact differ little from those in an unobstructed case (Fig. 1a). Therefore a normally functioning non-decompensating bladder could certainly empty to completion through these obstructed urethras.

In order to confirm this observation quantitatively, the association between the volume of residual urine and the detrusor pressure measured as flow ceases at the end of voiding has been examined. A significant positive correlation would provide evidence that the pressure demanded by the urethra was important in determining the volume of residual urine. In fact, for the 117 unoperated patients, the correlation coefficient was only 0.15, which was not significantly different from zero at the 5% level. (For comparison, the coefficient of correlation between the volume of residual urine and the maximum flow rate is −0.45, significant at the 1% level.)

This evidence implies that residual urine is not the direct, mechanical result of urethral obstruction but is the sign of an abnormality of bladder function, such that the bladder ceases contracting adequately before it is empty (decompensates). This view is consistent with that of Turner-Warwick *et al.* (1973) that residual urine can be a sign of bladder failure, secondary to outlet obstruction. However, it sometimes occurs in the absence of outlet obstruction.

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Applied Diagnostic Techniques: A Decisive Factor in the Long-term T-year Survival Rate in Prostatic Carcinoma

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Summary—It is shown from statistical data reported to the Swedish Cancer Registry that in cases of prostatic carcinoma the long-term T-year survival rate is the final outcome of a complex interplay of multiple factors including diagnostic technology and techniques for staging and grading. Assessment of the value of specific therapy is not possible except in controlled clinical trials. The T-year survival rate *per se* does not give an accurate estimate of the effect of treatment.

Results of therapy in oncology are often assessed by the long-term T-year survival rate in a group of consecutive patients. The effect of treatment is then assessed by comparison with a control group. Ideally, the treatment should be tested in a controlled clinical trial, but such trials demand large resources and the number of patients and the prolonged follow-up period necessary are generally prohibitive for a single centre. Thus the so-called historical control will often be selected as a control group.

Prostatic carcinoma is the most frequently occurring malignant disease in males in Sweden. Oestrogen treatment has been available since 1941 and when compared to historical controls, oestrogen-treated patients have an increased 5-year survival rate (Nesbit and Plumb, 1946; Nesbit and Baum, 1950; Fergusson, 1958; Jönsson *et al.*, 1963; Jönsson, 1971). When tested in a controlled clinical trial, however, oestrogen treatment was reported to be inferior to placebo in Stages I, II and III, while no difference was reported in Stage IV patients by the Veterans Administration Cooperative Urological Research Group (VACURG) (1967). The results of this controlled clinical trial differ from the results of studies based on historical controls. In the VACURG trial the results of placebo treatment were superior to those found with historical controls and comparable to the results ascribed to oestrogen treatment contemporary in uncontrolled trials. This may indicate that the improved survival rate is caused by factors other than oestrogen therapy.

The diagnostic approach to prostatic carcinoma was revolutionised in Sweden by the introduction of fine-needle transrectal aspiration biopsy (Franzen *et al.*, 1960), a technique which gained rapid acceptance, and a unique opportunity thus exists to determine whether the introduction of this diagnostic technique has affected the survival rate from the disease. This can be ascertained easily, albeit indirectly, from a study of population statistics available from the Swedish Cancer Registry.

Material and Methods

Statistics on prostatic carcinoma reported by the National Board of Health and Welfare (1959-1975) have been examined. Data on lesions reported to the Registry, classifications, principles of data collecting and processing are given in the Registry reports. These principles have remained essentially unchanged throughout the period 1958 to 1971. Statistics on the incidence of fine-needle aspiration biopsy as the basis for diagnosis were supplied by the Registry. The mortality rate in prostatic carcinoma was obtained from the National Central Bureau of Statistics (1959-1973).

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Table 1 Incidence, Age-Adjusted Incidence, Mortality and Age-Adjusted Mortality from Prostatic Carcinoma, Given as Numbers of Patients, in Sweden Between 1958 and 1971. The Numbers of Patients with Prostatic Carcinoma Diagnosed by Cytology Alone and by Methods Other than Cytology are also Shown

Year	*Incidence*	*Age-adjusted incidence*	*Mortality*	*Age-adjusted mortality*	*Diagnosed by*	
					Cytology alone	*Other methods*
1958	1494	1494	931	931	6	1488
1959	1549	1491	964	943	11	1538
1960	1544	1579	1003	960	13	1531
1961	1587	1498	1040	979	24	1563
1962	1830	1695	1124	1036	50	1780
1963	2005	1824	1198	1087	94	1911
1964	2341	2092	1191	1062	140	2201
1965	2299	2015	1114	969	238	2061
1966	2335	2026	1128	969	349	1986
1967	2602	2185	1180	984	495	2107
1968	2724	2249	1204	990	601	2123
1969	2885	2304	1307	1052	675	2210
1970	2852	2294	1264	1003	809	2043
1971	2997	2329	1401	1077	975	2022

Statistical terms

Incidence of Prostatic Carcinoma The number of patients registered in Sweden during the year T.

Mortality from Prostatic Carcinoma The number of patients registered as having died from the disease in Sweden during the year T.

Age-Adjusted Incidence and Age-Adjusted Mortality in the year T were calculated from the 1960 census of the population of the 5 Nordic countries (Norway, Sweden, Denmark, Finland and Iceland). The mathematical formula used by the National Board of Health and Welfare (1959-1975) was applied.

The following regression equations were calculated according to the method of least squares:

(1) The age-adjusted incidence on time.
(2) The age-adjusted mortality on time.

The following correlation coefficients were calculated according to the method of least squares:

(1) The correlation coefficient between the age-adjusted incidence and mortality rates.
(2) The correlation coefficient between the proportion of patients diagnosed by cytology only and the age-adjusted incidence.

The statistical significance of the correlation coefficient was tested by Student's t-test:

$$t = \frac{r\sqrt{n-2}}{\sqrt{1-r^2}} \qquad v = n-2$$

where

r = correlation coefficient
n = number of observations
v = degrees of freedom

Results

Incidence, age-adjusted incidence, mortality, age-adjusted mortality, number of patients diagnosed by cytology only and the number of patients diagnosed by other techniques are tabulated in Table 1.

The following regression equations were calculated:

(1) Age-adjusted incidence = 76 T + 1356 (Fig.).
(2) Age-adjusted mortality = 6 T + 958 (Fig.).

where $T_{1958} = 1$; $T_{1959} = 2$, etc.

The correlation coefficient between the age-adjusted incidence and mortality rates was 0.50 ($t = 1.99$; not significant).

The correlation coefficient between the proportion of patients diagnosed by cytology only and the age-adjusted incidence was 0.91 ($t = 7.68$; highly significant; $P < 0.001$).

The distribution of cases between different age groups remained essentially unchanged between 1958 and 1971 (Table 2). Thus a proportionate increase occurred in all age groups except the last one. The disproportionate increase in the last age group was less than 5%.

The incidence of prostatic carcinoma was positively correlated to the development level of local

Table 2 The Age-Specific Incidence of Prostatic Carcinoma in 1958 and 1971 Given as a Percentage of the Total Incidence in Each Year

Age group (years)	*1958 (%)*	*1971 (%)*
40-44	0.07	0.03
45-49	0.40	0.27
50-54	1.20	1.13
55-59	3.61	4.07
60-64	8.84	9.61
65-69	15.86	15.82
70-74	26.10	22.09
75-79	21.69	21.35
80-84	16.67	15.32
85-	5.56	10.24

medical services. The 1971 crude incidence rate (number of cases per million males per year) was 995 in Stockholm, 697 for Sweden except for the 3 large cities, and 458 in Norrbotten. Norrbotten is the least developed county in Sweden. Here the same rate was observed in 1971 as for the whole of Sweden in 1958.

Discussion

The incidence of prostatic carcinoma in Sweden doubled from 1958 to 1971. This was partly due to the fact that the number of persons at risk increased in Sweden during this period. However, the age-adjusted incidence rates showed a real increase in the incidence of diagnosed cases of prostatic carcinoma. In the short term, only random variabilities would be expected in incidence and mortality from a neoplastic disease. The mortality rate and the number of patients diagnosed by methods other than cytology did show random variability as expected, but the large increase in the age-adjusted incidence was not correlated with the age-adjusted mortality and cannot be interpreted as being due to random variability only.

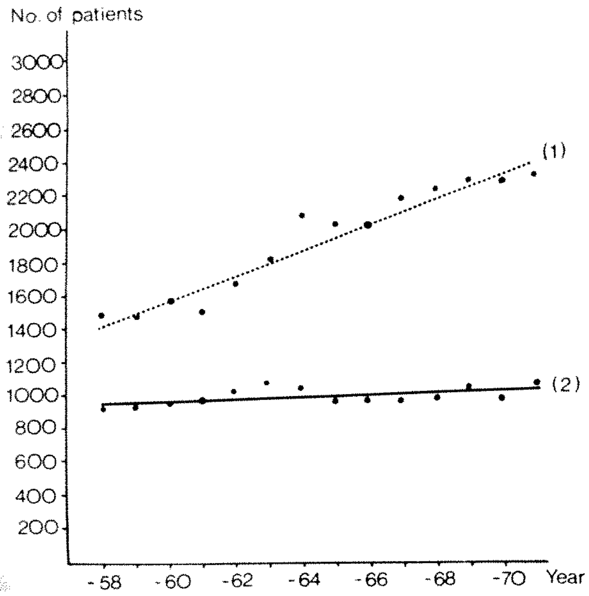

Fig. Age-adjusted incidence (1) and age-adjusted mortality (2) from prostatic carcinoma in Sweden between 1958 and 1971. The number of patients and regression lines are shown.

The interesting geographic variability which was found indicates that the incidence may be positively correlated with the development of local medical services. The highly significant correlation between the proportion of patients diagnosed by cytology and the age-adjusted incidence indicates a strong association.

In a histopathological autopsy study, Lundberg and Berg (1970) found prostatic carcinoma in 42.9% of 308 consecutive male autopsies. The diagnosis was completely unknown prior to death in 87.9% of the subjects. Thus the patients with symptomatic prostatic carcinoma represent only the "tip of the iceberg". There are a great many more with asymptomatic disease.

In Sweden, the period between 1960 and 1970 was one of remarkable economic development and medical services were greatly improved. Regular health controls, including rectal digital examinations, became routine among males aged over 50, especially in the larger cities. Fine-needle aspiration biopsy, while being simple and inexpensive, involves a considerable degree of precision (Ekman *et al.*, 1967) and it was widely performed. Thus its increasing application, backed by a strong belief in the prospects of "endocrine control therapy", resulted from the expansion of medical services which took place during this period. According to Lundberg and Berg (1970), the probability of a positive cytological diagnosis of prostatic carcinoma in the population was very high (38%) within the defined age groups, and the real achievement was to reveal a little more of the "iceberg".

The diagnosis will be made in only a small minority of males with histopathological prostatic carcinoma. This minority (the "waterline" of the "iceberg") is at all times defined by specific diagnostic techniques applied under specific circumstances, and the observed incidence rates have therefore varied throughout medical history.

Until the early part of the nineteenth century all prostatic enlargement was considered malignant (Baillie, 1794). Improved autopsy techniques reversed the situation and Thompson (1873) declared that prostatic carcinoma was a very rare disease. In Sweden today it is the most commonly found malignant disease in males.

Although there was an increase in the number of patients diagnosed after 1958, the mortality rate remained constant during the period. The life expectancy in these additional patients was equal to that of the male Swedish population within the defined age groups. As the increase occurred in all age groups, the overall prognosis in these additional cases should be excellent. The improved diagnostic techniques, plus their widespread application, resulted in proportionally fewer patients being given a poor prognosis. If the influence of all other factors is assumed to be equal, the long-term T-year survival from prostatic carcinoma would certainly have increased during the period for this reason alone.

Two clinical trials were conducted at the same Swedish centre during this time. Jönsson *et al.* (1963) reported a 41% 5-year survival rate in 105 patients treated with polyestradiolphosphate (Estradurin, LEO). In a later study Jönsson (1971) reported a 61% 5-year survival rate in 126 patients treated with a combination of polyestradiolphosphate and ethinylestradiol (Etivex, LEO). The improved results in the 1971 study were claimed to be due to superior treatment.

This interpretation of the results had far-reaching consequences. Treatment with a combination of Estradurin and Etivex subsequently became standard therapy for prostatic carcinoma in Sweden, and replaced other forms of oestrogen treatment. Furthermore, as the results in Stages I and II were comparable or even superior to the results reported with radical surgery, the need for surgery was questioned and radical prostatectomy is not performed in Sweden today.

The way in which results were interpreted in these reports highlights the fallacies involved in the use of historical controls. As already mentioned, the long-term T-year survival rate improved because patients with a poor prognosis became increasingly mixed with patients with an excellent prognosis. Provided that the patients in these studies were sampled at random, therefore, the superior results of the 1971 study, when compared to those of the historical controls 8 years previously, can be shown to be wholly due to the fact that different populations, defined by a different diagnostic technology, were sampled.

The results of the present study indicate that the use of historical controls, although believed to be highly comparable, may in fact be seriously misleading. Thus, while earlier diagnosis led to significant improvement in the T-year survival rate in patients with prostatic carcinoma, the credit for this was erroneously given to treatment. As the number of patients with prostatic carcinoma who will never develop symptoms of malignancy greatly exceeds those with symptomatic disease, the age-specific T-year survival rate theoretically attainable (provided *all* males are examined prophylactically at appropriate intervals) probably approaches that of the normal male population. Given this background, it should be emphasised that the concepts of *survival* and *results of treatment*, although often confused, are logically independent. The belief that early diagnosis has a critical influence on the result of therapy may, unless proved otherwise in controlled clinical trials, be erroneous and arise from neglect of the simple fact that *registered survival* may not be a measure of the *effect of treatment* but is primarily determined by the growth rate of the tumour and the time when registration began.

Before the endocrine era, Nesbit and Plumb (1946) reported a 10% 5-year survival rate in Stage III patients. The VACURG (1967) trial reported a 54% 5-year survival rate in the same stage with patients on placebo. Most patients studied by Nesbit and Plumb were staged prior to the acid phosphatase test and the arrival of scintigraphic techniques. The discrepancy in the results may be explained if it is assumed that a proportion of cases reported to be in Stage III by Nesbit and Plumb would have been transferred to Stage IV if assessed by the staging facilities available to VACURG (1967). Thus, to the extent that staging techniques vary, the assumption that factors other than therapy can be controlled by staging is not valid. Staging does not justify the use of historical controls. Furthermore, it may be shown that improved diagnostic techniques, together with improvement in staging techniques, tend to keep the proportion of cases in different stages unchanged.

Survival in neoplastic disease is the final outcome of a complex interplay of multiple factors and stage, grade, techniques for staging and grading, time of and facilities for diagnosis, age distribution in the population sampled, biological, social, random and unknown variability may be of importance. In order to assess the value of a specific therapy controlled clinical trials will have to be performed. Simply to assume that the T-year survival rate gives a correct estimate of the effect of treatment is to assume that all other factors are invariable. The problem is not that simple.

Conclusions

Patients with diagnosed prostatic carcinoma represent only the "tip of the iceberg". There are a great many more asymptomatic males who will never be diagnosed. In Sweden, transrectal fine-needle aspiration biopsy for cytological diagnosis was used with increasing frequency after 1960. Statistics from the Swedish Cancer Registry support the conclusion that the main effect of this diagnostic progress was to make a larger part of the "iceberg" visible. Thus the increase in the age-adjusted incidence of prostatic carcinoma in Sweden between 1958 and 1971 was primarily caused by changes in applied diagnostic techniques. Available evidence indicates that the "real" or "biological" occurrence of prostatic carcinoma, apart from random variability, remained constant.

The main effect of these changes was to expand, in a non-random fashion, the population of patients with diagnosed prostatic carcinoma. Thus patients with a poor prognosis were increasingly mixed with those with an excellent prognosis.

The overall result, a relative decrease in mortality from prostatic carcinoma, was registered in contemporary, uncontrolled clinical trials. Here, an improved T-year survival rate was misinterpreted as being caused by a specific treatment. As a result, this treatment came to be regarded as superior to other forms of treatment and became standard throughout the country.

The long-term T-year survival rate is dependent upon a great many factors and should not be accepted merely as a measure of the effect of treatment. The results of treatment in prostatic carcinoma should be assessed only from controlled clinical trials.

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Has the Suprapubic Suspension Operation any Influence on the Urethral Pressure Profile?

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Summary—The urethral pressure profiles of 35 patients suffering from stress incontinence before and after suprapubic suspension operations have been analysed.

Irrespective of the post-operative result there were no significant changes in the various characteristics of the pressure profile.

The results suggest that a suspension operation for stress incontinence has no direct effect on the sphincteric urethral mechanism but places the urethra in a higher position where it can be affected by increases in intra-abdominal pressure.

In stress incontinence an increase in intra-abdominal pressure results in leakage of urine because the total bladder pressure exceeds the urethral pressure. The urethral pressure profile has been shown to undergo certain changes in patients suffering from stress incontinence. Gleason *et al.* (1974) found a reduction of the "continence zone" and a decrease in the mean urethral closure pressure. Andersen and Bradley (1977) noted also a diminution of the maximum urethral closure pressure and a shortening of the functional urethral length. After a suspension operation most patients are continent. Marshall and Segaul (1968) reported a success rate of 86% in the first months following operation, although this decreased with time.

There is still no unanimity about the mechanism involved in the achievement of continence following suprapubic suspension. Enhörning and Westin (1963) illustrated the importance of pressure transmission from the abdominal cavity to the urethra as a mechanism for normal closure. Tanagho (1976) claimed that continence would be regained by restoration of the sphincteric mechanism (which he believed to be intact) to its proper position, because its efficiency was impaired as a result of weakness of its support. According to Hutch (1972), continence was regained by elevation of the bladder neck to a position where the base plate once again could assume its normal flat position. As long as the base plate remained flat, the bladder neck was closed and the patient continent. During micturition there was a funnelling of the base plate. Because of sphincteric weakness the base would never be flat, even at rest, and in such situations the patient was continent only as a result of the urethral tone. This was sufficient for continence at rest, but not during stress, because rises in intra-abdominal pressure, which were normally intercepted by the flat base plate, were no longer intercepted because the base plate was insufficient.

We were interested in determining whether surgical procedures aimed at fixation of the urethra in a higher position have any influence on the urethral closure pressure. This problem prompted us to compare the pressure profiles of patients before and after colpocystourethropexy.

Patients and Methods

From December 1975 to July 1977 43 patients underwent a suprapubic suspension operation for stress incontinence. Although the pre-operative cystometrogram showed a discrete bladder instability in 4 patients, because of associated predominant sphincteric weakness a suspension procedure was thought to be reasonable. The age of the patients varied between 24 and 75 years with a mean of 46. Eighteen patients had had no previous operation, while the remaining 25 had been referred following one or more unsuccessful operations for incontinence. Six patients were

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Table 1 Mean Functional Urethral Length in cm According to Age Groups in 35 Patients

Age group	*-30*		*31-40*		*41-50*		*51-60*		*61-70*		*70+*	
	B	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*
Supine—empty	3.3	3.6	3.4	3.4	2.9	3.1	2.3	2.9	2.1	3.4	2.6	3.7
Supine—full	3.1	3.2	2.6	3.0	2.6	2.9	2.1	2.6	2.1	3.0	2.2	2.8
Standing—full	2.6	2.9	2.5	2.7	2.5	2.6	1.7	2.3	1.6	3.0	2.4	
Number	5		7		11		8		3		1	

B = Before operation; A = After operation.

lost to follow-up and 2 others had undergone a ureteroileostomy because of intractable incontinence.

Pre-operative investigations included a thorough history with special attention to previous abdominal and/or vaginal operations. All patients had a full urine and blood examination, cystoscopy, IVP and cystography with lateral views, at rest and on straining, in order to determine the degree of bladder descent. Cystometrograms were performed in all patients to exclude bladder instability.

The urethral pressure profile was measured according to the method described by Brown and Wickham (1969). An 8 FG catheter with 2 side-holes 5 cm from the closed tip and an opening 1 mm in diameter was introduced into the bladder and mechanically withdrawn at a rate of 1 mm/s. The perfusion rate was 2 ml/min. The recording paper moved at a speed equal to that of catheter withdrawal. The urethral pressure profile was measured with an empty and a full bladder (±300 cc), in the supine and in the upright position, at rest and in stimulated stress situations where the patient was asked to cough every 5 s. Abdominal pressure was measured with a rectal catheter.

Follow-up urethral pressure profiles were performed between 1 and 20 months following operation. In most of the patients a Parent modification of the Marshall-Marchetti-Krantz operation (Parent, 1973) was performed, while more recently patients underwent a Burch suspension (Burch, 1961).

Results

Clinical

Of the 35 patients available for follow-up 23 (66%) are continent, and this group includes all of the 18 new cases. Six patients show some incontinence only during excessive stress, 4 are still incontinent (although to a lesser degree than before operation) and 2 patients remain unchanged.

Urethral Pressure Profile

The main urethral length, the urethral closure pressure and shape of the profile were studied.

Mean Functional Urethral Length Table 1 shows the mean functional length in the 35 patients before and after operation as measured in the supine position with empty and full bladder and in the standing position with full bladder. The mean urethral length in healthy women is 3.5 cm with a standard deviation of ±0.6 (Edwards and Malvern, 1974). In sphincteric weakness this is 3.5 cm ± 0.9. Table 2 shows the results obtained in the 18 new cases measured under the same conditions. Here we found identical changes.

Maximum Urethral Pressure Amplitude Table 3 shows the maximum urethral pressure amplitude of the 35 patients before and after operation as measured in the supine position with empty and full bladder and in the standing position with full bladder. According to Edwards and Malvern (1974) the mean urethral closure pressure in healthy patients can be calculated as follows:

Table 2 Mean Functional Urethral Length in cm According to Age Groups in 18 Patients Without Previous Operation

Age group	*-30*		*31-40*		*41-50*		*51-60*	
	B	*A*	*B*	*A*	*B*	*A*	*B*	*A*
Supine—empty	3.3	3.6	3.5	3.5	3.0	3.2	2.5	3.0
Supine—full	3.1	3.2	2.7	3.1	2.9	2.9	2.1	2.8
Standing—full	2.6	2.8	2.4	2.9	2.6	2.6	2.2	2.4
Number	4		3		6		5	

B = Before operation; A = After operation.

Table 3 Maximum Urethral Pressure Amplitude in cm H_2O According to Age Groups in 35 Patients

Age group	*−30*		*31-40*		*41-50*		*51-60*		*61-70*		*71+*	
	B	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*
Supine—empty	50	35	72	61	63	57	50	46	48	42	33	22
Supine—full	44	38	61	58	63	52	54	45	53	34	35	15
Standing—full	50	34	67	67	56	53	60	48	33	44	22	
Number	5		7		11		8		3		1	

B = Before operation; A = After operation.

amplitude in cm = 92 − age of the patient in years. If the observed amplitude is less than the calculated value the diagnosis of sphincteric weakness can be established in 66% of cases. After operation there was a decrease in the maximum urethral pressure amplitude with empty bladder as well as after bladder filling and in the upright position.

Table 4 shows the results obtained in the 18 new cases measured under the same conditions. We have no clear explanation for the discrepancy noted in column 5 of this table (90 cm H_2O).

We also examined the pressure profiles of patients who failed to benefit from the operation in order to detect whether such failures could be explained urodynamically. The results are shown in Table 5. As can be seen, the changes in this group resembled those observed in the whole group as well as in the successfully treated new cases.

Shape of the Profile Analysis of the curves of the various groups showed no change in the general shape and pattern before and after operation.

Discussion

The results in our study have shown that suprapubic suspensions, irrespective of the clinical success rate, have little influence on the functional urethral length, the maximum closure pressure and the shape and pattern of the profile. The tendency to an increase in the functional urethral length and a decrease in the maximum urethral closure pressure was found in all patient groups and was not significantly different. With bladder filling, supine, and in the erect position with the bladder full, we noted a decrease in urethral length as a result of "vesicalisation" of the urethra both before and after repair. In contrast, in healthy women the functional length increases when changing from the supine to the upright position (Henriksson *et al.*, 1977), probably because the muscles of the pelvic floor contract and thus the urethra lengthens. Our findings were similar to those of Edwards and Malvern (1974) who found a decrease in the urethral length with increasing age. In healthy women there is a gradual increase in urethral pressure (Griffiths, 1973) on bladder filling due to stretching of the urethral muscle, secondary to the vesical distension (Ghoneim *et al.*, 1975). After operation there was a decrease in the maximum urethral pressure profile and here again our results support the findings of Edwards and Malvern (1974), who also noted a fall in the profile amplitude with increasing age.

Table 4 Maximum Urethral Pressure Amplitude in cm H_2O According to Age Groups in 18 Patients Without Previous Operation

Age group	*−30*		*31-40*		*41-50*		*51-60*	
	B	*A*	*B*	*A*	*B*	*A*	*B*	*A*
Supine—empty	50	36	74	70	63	62	59	56
Supine—full	44	38	73	71	59	57	64	54
Standing—full	51	34	64	73	45	57	90	54
Number	4		3		6		5	

B = Before operation; A = After operation.

Table 5 Pressure Profile of the 13 Failures

	Mean functional urethral length		*Maximum urethral pressure amplitude*	
	B	*A*	*B*	*A*
Supine—empty	2.6	3.0	46	38
Supine—full	2.2	2.7	45	39
Standing—full	2.0	2.6	49	41
Number	13		13	

A = After operation; B = Before operation. As previously mentioned, all of the 13 patients had already undergone one or more operations.

This is not surprising since the urethral sphincter in women, consisting of bladder neck, urethral smooth muscle, paraurethral striated muscle of the urogenital diaphragm, submucosal vessels and the mucosa, is not directly involved in the surgical repair. The experimental findings of Mayo and Hinman (1973) seem to lend support to our clinical measurements. These authors found that when the urethra was mechanically lengthened urethral closure was decreased, and they concluded that suspension operations reduce stress incontinence because they help to prevent permanent funnelling of the bladder neck (Tanagho *et al.*, 1968) and because they place the urethra in a higher intra-abdominal position so that it can receive its normal share of intra-abdominal pressure when this is raised (Enhörning and Westin, 1963). This will finally result in a urethral pressure which remains, during stress, higher than the bladder pressure and thus there will be no loss of urine. Our study and the findings of Mayo and Hinman (1973) contradict the widely held view that mechanical lengthening of the urethra increases urethral closure pressure (Harrison and Paterson, 1970), whether this is achieved by tightening the helically arranged fibres of the female urethra (Mitchell, 1972; Yeates, 1972) or not.

From this study we also conclude that following an unsuccessful suprapubic suspension a further suspension procedure is worthwhile, but there is no need to repeat the urethral pressure profile. Indeed, knowing that in patients with sphincteric weakness there is a decrease in the maximum closure pressure, and knowing the changes that occur after suspension, a urethral pressure profile is not required in these circumstances.

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Lateral Curvature of the Erect Phallus Without Chordee

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Summary—Three cases of lateral curvature of the penis during erection are described. In no case was there evidence of chordee. A corrective operation for this condition is described.

Curvature or deviation of the penis during erection is in most cases due to chordee in association with hypospadias, congenital short urethra, urethra duplication, Peyronie's disease or certain forms of urethritis.

A much rarer type of phallic curvature occurs in the absence of chordee. In the flaccid state the penis looks and feels normal with no, or perhaps minimal, deviation. However, during erection it adopts a marked curvature, making sexual intercourse difficult, if not impossible. In the 3 cases reported here the curvature was lateral so that during erection the phallus was banana-shaped.

Longitudinal curvature without chordee has been described (Nesbit, 1965).

Case Reports

Case 1. J.M., a 25-year-old man, was referred by a Marriage Counselling Bureau. He had been married for 1 year, during which time he had been unable to achieve vaginal penetration. The patient volunteered the information that, since puberty, his penis tended to assume a banana-shaped appearance during erection, with convexity to the right.

On examination he was a healthy-looking young man. The genitalia looked and felt normal. In particular, the flaccid penis showed no evidence of chordee, urethral shortening, fibrosis or Peyronie's disease. The erect penis showed a lateral curvature with the convexity to the right.

In view of the absence of any obvious phallic pathology it was felt that this condition was more likely to be due to congenital asymmetry of the corpora cavernosa than to tethering of the shorter, concave side by fibrosis. Accordingly, with the patient's concurrence, it was decided to attempt to shorten the longer, convex corpus, thus restoring equality in length of the corpora during erection.

At operation, the absence of fibrotic bow-string tethering on the shorter, concave side was confirmed. The operation was carried out as described below. In the immediate post-operative period there was marked oedema of the penis and scrotum which gradually settled down over a period of 10 days. Subsequent erection resulted in a practically straight penis although there was still a very slight residual deviation. The patient was able to have satisfactory intercourse 5 weeks after operation. The couple have since had a child. Five years after operation the slight residual curvature has become somewhat more obvious but the erect penis has remained generally straight in outline and the patient is very satisfied with the result.

Case 2. A 29-year-old bachelor was referred for "impotence" by his general practitioner. On questioning, it transpired that the patient was not impotent but, in fact, had good erections with lateral curvature of the penis, convex to the right. He had always been shy about mentioning this and was obviously very depressed about the anomaly.

On examination the penis looked normal with no evidence of chordee. A pencil tracing of the erect penis confirmed the lateral curvature.

A corpus spongiosum shortening procedure was undertaken with a deliberate attempt slightly to over-correct the curvature. Apart from the expected penoscrotal oedema, the post-operative course was uneventful. Within 6 months the slight over-correction had straightened out and 3 years later the patient still has straight erection. A noticeable effect of the operation has been the psychological uplift to his morale.

Case 3. A 43-year-old man, who was undergoing treatment for acromegaly, complained of lateral curvature of his penis during erection. He had been able to have intercourse but with some difficulty. The disability had recently worsened and the erect penis showed a definite curvature to the left. He refused surgical treatment.

The Operation

The operation is preferably done under general anaesthesia with the patient catheterised.

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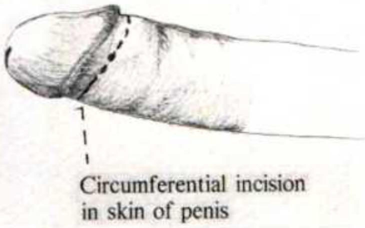

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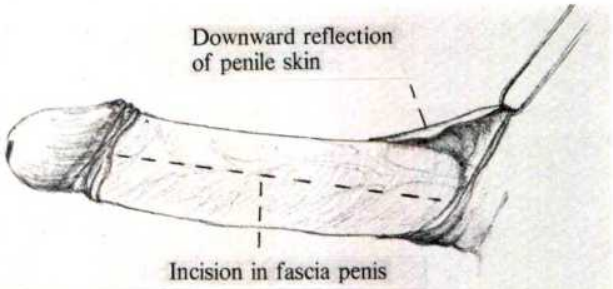

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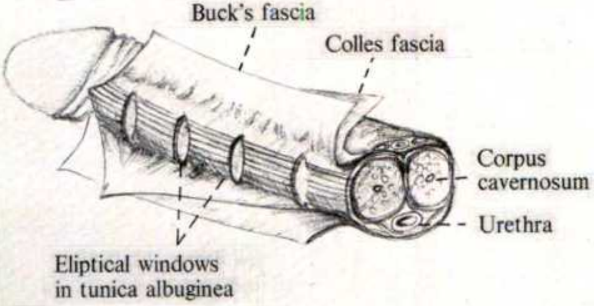

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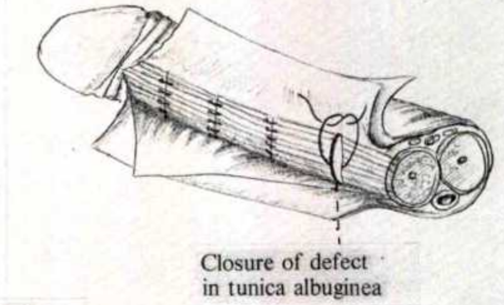

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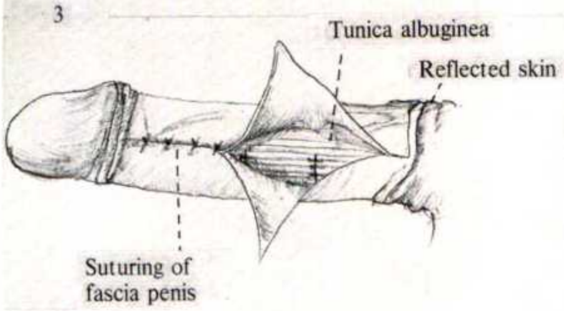

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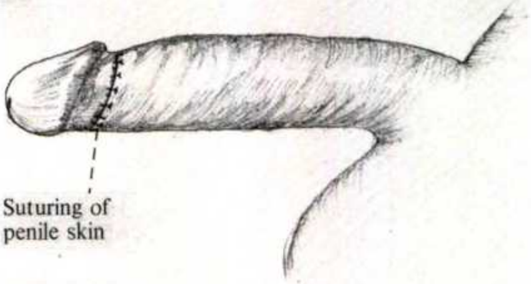

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Under light anaesthesia an erection is induced so that an assessment can be made of the amount of shortening required.

A circumferential incision is made around the corona glandis (Fig. 1). The entire penile skin is reflected to the base of the penis. Both corpora cavernosa and the corpus spongiosum are palpated in their entirety. In none of the above cases was there any evidence of fibrosis or other abnormal tissue.

A straight longitudinal incision is made in the fascia penis, extending along the whole length of the shaft on the side to be shortened (Fig. 2).

Using fine dissecting forceps and scissors a number of vertical elliptical windows (usually 5 or 6) are cut in the tunica albuginea overlying the corpus cavernosum (Fig. 3), great care being taken to avoid damaging the erectile tissue by lifting the tunica albuginea off the thin fascial membrane investing the erectile tissue. A gap of 1.5 to 2.5 cm is left between the defects, the exact spacing depending on the length of the penis and the amount of correction necessary. It is advisable slightly to over-correct the curvature to counteract the natural tendency of the erect phallus to deviate towards the original curvature.

The edges of the elliptical defects are then closed with interrupted No. 1 propylethylene sutures (Fig. 4).

An attempt is made to check the correction of the curvature by inducing erection under light anaesthesia or by injecting saline into the erectile tissue.

The fascia penis is then sutured with interrupted catgut sutures (Fig. 5) and the reflected penile skin is drawn forward and sutured to the skin fringe around the corona glandis (Fig. 6).

A paraffin gauze dressing is wrapped around the penis, over which is placed a gauze dressing held in place by adhesive strapping. A scrotal support is applied.

The urethral catheter is removed when the postoperative oedema starts to subside, usually within 2 or 3 days.

Intercourse can usually be allowed 5 weeks after the operation. The patient should be followed up at 4-monthly intervals for 1 year.

Discussion

The congenital deformity observed in these 3 cases should be differentiated from true chordee of the penis since it was caused entirely by an asymmetry of the dimensions of otherwise normal corpora cavernosa.

The condition may not be as uncommon as would appear at first sight. A salient feature in 2 of the 3 cases described was the patient's reluctance to seek medical advice.

Detection of this condition is unlikely on routine medical examination as the penis looks and feels normal in the flaccid state. More awareness of the anomaly, particularly in men who have difficulty in achieving normal intercourse, may bring more cases to light.

In the absence of fibrotic tethering of the affected side it would be futile to attempt lengthening of this side. Shortening of the longer side, as described above, has given good long-term results. No damage to erectile tissue nor to vessels or nerves has occurred. Slight over-correction of the curvature is advisable. To achieve this, inspection of the erect penis before and during operation is helpful, though not always feasible.

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Primary Malignant Melanoma of the Penis. Two Cases and a Review of the Literature

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Summary—Two cases of primary malignant melanoma of the penis are reported and 35 cases from the world literature are reviewed. The tumour most commonly started in the glans penis and less frequently from the prepuce. The microscopic appearances were identical with those of tumours arising elsewhere in the skin. A comparison is made between the incidence of melanoma of the penis and melanoma occurring elsewhere on the body surface.

Evaluation of the best treatment was difficult because the total number of cases was small and the methods of treatment and results so variable.

It would seem that the prognosis of malignant melanoma of the penis is generally poor, although there are sufficient examples of long-term survival after total amputation in Stage I disease to suggest that this radical treatment is justified.

Malignant melanoma of the penis is rare and accounts for about 1% of cases of squamous cell carcinoma of the penis (Dixon and Moore, 1953). Thirty-five cases have been reported in the last 106 years. Joelson (1924) reviewed the world literature from 1871 to 1924 and found only 8 cases; since then further cases have been reviewed by Wheelock and Clarke (1943), Paquin and Roland (1956), Reid (1957), Schneiderman *et al.* (1965), Patoria and Junnarkar (1966), Thomas and Fenn (1967), Fronstin and Hutcheson (1969), Gojaseni and Nitiyant (1972), and Bracken and Diokono (1974).

Case 1

A 72-year-old, married, white male was admitted to Bristol Royal Infirmary complaining of a swelling on the glans penis which had been present for many years but 3 months prior to admission had developed a serious discharge and black discolouration. On examination the patient was ill and had a dark tumour on the tip of the penis. The distal shaft of the penis was clinically involved in a tumour mass whilst both the tumour and the groin nodes were palpable and tender. The liver was enlarged. Laboratory investigations were normal except for iron deficiency anaemia, but a chest X-ray showed lung metastases. Biopsy of the tumour revealed primary malignant melanoma developing from a junctional type of naevus (Fig. 1). The patient underwent palliative partial amputation of the penis but he gradually deteriorated and died 4 months later.

Case 2

A 42-year-old, white male was admitted with a small dark preputial lesion of 2 months' duration. Physical examination revealed anaemia, hepatomegaly and a dark ulcer 2 × 3 cm on the foreskin and glans penis, but not involving the urethra. Both sets of inguinal

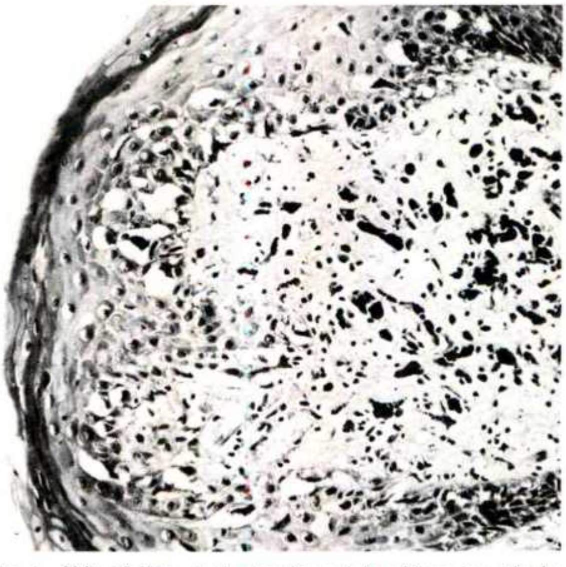

Fig. 1 Skin of glans penis showing origin of invasive, highly pigmented tumour cells overlying epidermis. (HPF ×240.)

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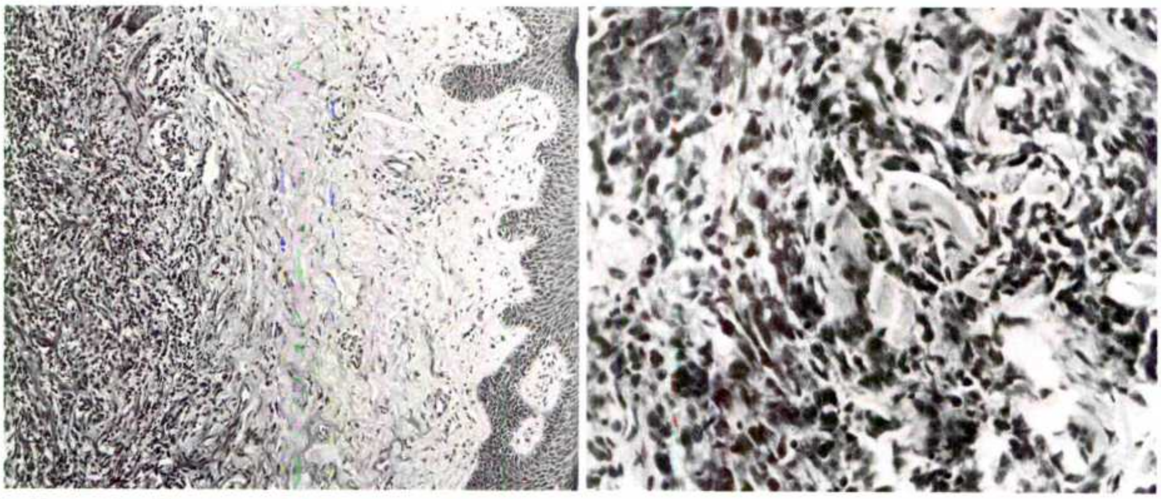

Fig. 2 (a) Foreskin, showing diffuse round cell infiltration and melanocytes. (HPF ×110.) (b) Selected part of (a) showing highly pigmented neoplastic cellular infiltration. (HPF ×275.)

lymph nodes were enlarged. Chest X-ray and liver scan both revealed multiple metastases. Biopsy of the tumour and inguinal lymph nodes revealed a primary malignant melanoma with metastatic spread to the lymph glands (Fig. 2). The patient underwent a palliative partial amputation and Bacillus Calmette-Guerin immunotherapy. He improved for 8 months after this therapy and further biopsy of the inguinal nodes revealed regression of the tumour. Shortly after this, however, he developed a recurrence in the stump of the penis and in the inguinal lymph nodes. At the same time he developed jaundice and died 13 months after starting treatment.

Discussion

Thirty-five cases of malignant melanoma of the penis have been reviewed in the world literature. The tumours were staged according to the classification described by Bracken and Diokono (1974). In Stage I the tumour is confined to the penis, in Stage II there are metastases to the regional lymph nodes and in Stage III there is direct extension of tumour to surrounding structures or distant metastases. The age incidence varied from 33 to 78 years (mean 66 years). The most common site was the glans penis (23 out of 28 cases) and 4 of these involved the external urethral meatus. The prepuce was next in order of frequency, while the shaft was involved in only one case (Das Gupta and Grabstald, 1965).

The race of the patient was mentioned in only 18 cases in the literature. Of these 13 were white and 5 were Asian (3 Indian and 2 Malay).

The microscopic appearances of melanoma of the penis are identical with those of melanomata arising elsewhere on the skin (Fig. 1). Metastases occur by lymphatic channels to the regional lymph nodes, by the blood stream to distant parts of the body such as lungs, liver, brain and bones, or by direct extension into the surrounding tissues. Comparing the incidence of malignant melanoma of the penis with that of the same tumour elsewhere on the skin, Das Gupta and Grabstald (1965) found 2 cases among 1200 malignant melanomata of the skin, whilst Cascinelli (1969) found only one example among 720 cases of malignant melanoma.

In a review of all malignant melanomata of the skin registered from Bristol Hospitals a total of

Table 1 Distribution of Primary Malignant Melanoma in the Male Patients Registered in the Cancer Registry from Bristol Hospitals

Site	*No. of patients*
Abdominal wall	3
Back and shoulder	58
Buttock	3
Chest wall and axilla	6
Ear	13
Eyelids	4
Face	49
Groin	4
Lower limb	49
Neck	5
Penis	2
Upper limb	22
Total	218

Table 2 Results of Treatments in 28 Patients

Treatment	*No. of patients*	*Stage I*		*Stage II*		*Stage III*	
		Cases	*Survival*	*Cases*	*Survival*	*Cases*	*Survival*
Partial amputation							
Alone	5	3	6 months; 18 months and 1 no follow-up	1	20 months	1	6 months
And block dissection	3	2	2 years; 1 died due to septicaemia 2 days later	-	-	1	4 months
And radiotherapy	1	1	1 year	-	-	-	-
And endolymphatic radiotherapy with Lipiodol 131	1	-	-	1	21 months	-	-
And immunotherapy	1	-	-	1	3 months	-	-
Total amputation							
Alone	6	4	4 months; 5 years; 8 years and 1 no follow-up	1	14 months	1	No follow-up
And block dissection	6	4	6 months; 9 months; 6 years and 10 years	2	5 months and 1 year	-	-
And block dissection and radiotherapy	3	-	-	-	-	3	8 months, 2 years and 2 years
None	2	-	-	1	8 months	1	2 months
Total	28	14		7		7	

808 cases (590 females and 218 males) was found. The distribution of these tumours on the skin of the male patients is shown in Table 1. In this series there were 2 melanomata of the penis among a total of 218 melanomata of the whole body surface (0.92%).

Many different methods of treatment had been applied in the cases reported in the literature. It was not possible to determine the treatment and results in 7 of these cases. Amongst the 14 examples of Stage I disease treatment by partial amputation alone, or in association with block dissection of the inguinal glands or radiotherapy, did not produce a single survival of more than 2 years. Total amputation, however, with or without block dissection, appeared to be more successful with 4 patients of the 8 reported as surviving for at least 5 years (Table 2).

When the disease process had reached Stages II or III only 2 patients from a series of 14 survived for 2 years after treatment by either partial or total amputation (Table 2).

From this review we conclude that these tumours commonly start in the glans penis and less frequently from the prepuce. It appears that the incidence of melanoma of penis is higher in white people. In spite of different kinds of treatment, control of the tumour and long-term survival have not been satisfactory and the prognosis is poor. There are, however, sufficient examples of long-term survival after total amputation in Stage I disease to suggest that this radical treatment is justified.

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Tumours of Testis in Jamaica

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Summary—Malignant tumours of the testis are reported to be rare in negroes. All cases reported in the records of the University Hospital of the West Indies and the Jamaica Cancer Registry over the period June 1958 to December 1976 were studied.

There were 26 cases, giving a world standardised incidence of 0.40 per 100,000 per year. This incidence is higher than that seen in African negroes but lower than that of negroes in North America. The peak age incidence is a decade later than that commonly seen in high incidence countries.

Tumours of the testis are uncommon malignant conditions with a varying incidence in different countries (Pugh, 1976). They are rare in negro populations (Prates and Torres, 1965). This study reports the incidence of these tumours in Jamaica, which has a predominantly negro population, and compares the findings with previously reported studies in Africa and America.

Patients

Twenty-six cases of tumours of the testis were reviewed over a 19-year period, June 1958 to June 1977. Twelve of the cases from Kingston and St Andrew district (male population 244,423) appeared in the Jamaica Cancer Registry. The remainder were from the rest of the island (male population 364,100).

Twenty-one case histories were available for examination and histological review. Two cases did not have histological confirmation of the diagnosis and have been excluded from our study. In 3 cases histological slides were not available for review. Twenty-three of the patients were negroes and one was Chinese.

Results

From 1958 to 1974 there was a comparatively regular presentation of one case each year. Then in 1975 and 1976 there were 6 and 4 cases respectively (Table 1).

Ten patients were in the 30 to 50 age group and 7 were over the age of 60 years (Fig.).

In all but one of the patients the presenting symptom was swelling of the testis. In one patient the tumour occurred in an undescended intra-abdominal testis. The right and left testes were equally affected and there was one case of bilateral tumour.

There was a 5-day to 6-week delay between the onset of symptoms and diagnosis and two-thirds of the cases had regional node involvement or distant metastases at the time of presentation.

The histological types of these testicular tumours were: seminoma (13); embryonic carcinoma (5); teratoma (1); Leydig cell (1); lymphosarcoma (1).

The patients were treated on conventional lines by orchiectomy followed by radiotherapy.

Discussion

The assessment of the incidence of the disease

Table 1 Incidence of Tumours of Testis in Jamaica June 1958-June 1977

Year	*No. of cases*		*Total*
June-June	*Histologically proved*	*Histologically not proved*	*No. of cases*
1958-1963	6	-	6
1963-1968	6	1	7
1968-1973	2	-	2
1973-1977	10	1	11
Total	24	2	26

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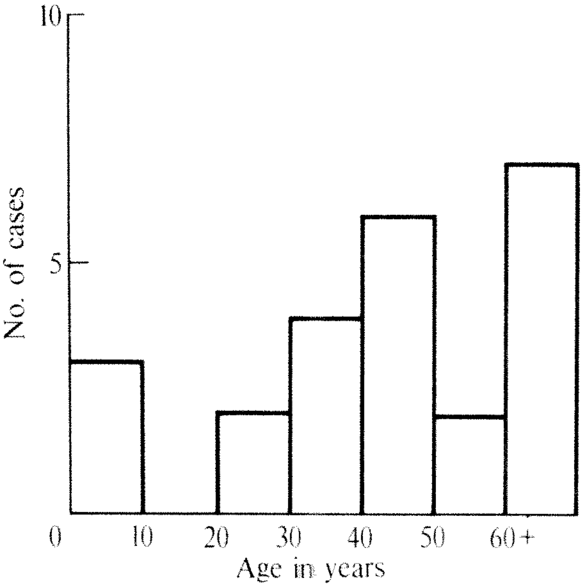

Fig. Age incidence of cancer of the testis in Jamaica.

must take into account the inherent problems of accuracy of diagnosis and notification, and in Jamaica there are sometimes problems in seeking and obtaining medical treatment. If the findings are restricted to the well documented part of the population covered by the Jamaica Cancer Registry (Kingston and St Andrew district), then the crude incidence of testicular tumours was 0.26 per 100,000 per year. This is in accord with the generally accepted low incidence in negro populations. Oettle (1964) reported 7 histologically confirmed cases in 2 million Bantu aged 15 to 54 years, during a 5-year period (1949 to 1953): in the same period, in contrast, he found 22 testicular tumours among 600,000 whites in the same age group. Davies *et al.* (1964), reporting from Uganda, found only 3 cases of testicular tumours for the period 1897 to 1956. Edington and Maclean (1965) reported 6 cases from Ibadan during the period 1960 to 1963. No testicular tumours were reported by Prates and Torres (1965) in Lourenco Marques, Portuguese East Africa, during the 5-year period 1956 to 1961. Tulinius *et al.* (1973), comparing different populations, found that testicular tumour occurred 20 times more frequently in whites than in negroes, whereas the USA National Cancer Institute found a negro: white ratio of 1:3.

When we compare the Jamaican figures with those reported for African populations, after the necessary adjustments for age variation between different populations (Doll *et al.*, 1966), we have a Jamaican incidence of 0.33 per 1000 males per year when corrected for the African population and 0.4 when corrected for the world population. Although this incidence is still low, this is higher than that reported in Africa despite the predominantly negro population in Jamaica (Table 2).

The peak age incidence of testicular neoplasia in Jamaica (Fig.) is earlier than that in North American negroes, in whom it is more commonly seen in the sixth decade (Grumet and MacMahon, 1958). However, it is of interest that our peak age incidence at 30 to 50 years is a decade later than that seen in high incidence countries (Clemmesen, 1969).

The relative importance of environmental or hereditary factors in the aetiology of testicular tumours is difficult to assess. It has been suggested that a high scrotal temperature may be a factor (Clemmesen, 1969). In Jamaica, a tropical country with a Westernised clothing habit, *it* could be postulated that the scrotal temperature

Table 2 Age-adjusted Annual Incidence Rates of Malignant Testicular Tumours per 100,000 Males in Certain Countries and Districts in the Early 1960s (Adjusted to World Standard Population). (Taken from Teppo, 1973)

Country or district	*Incidence rate*
Denmark	4.5
Federal Republic of Germany (Hamburg)	4.0
Norway	3.6
New Zealand (Maori)	3.4
Canada (Saskatchewan)	3.3
USA (Alameda, white)	3.1
South Africa (Cape Province, white)	2.6
Scotland	2.5
Sweden	2.2
England (Sheffield)	2.1
Colombia (Cali)	2.0
Hungary (Miskolc)	1.7
Yugoslavia (Slovenia)	1.6
Israel	1.5
Japan (Okayama)	1.2
Canada (Quebec)	1.1
Hungary (Szabolcs, Szatmar)	1.0
Poland (Cracow)	1.0
Romania (Banat)	1.0
Finland	0.9
India (Bombay)	0.9
South Africa (Cape Province, coloured)	0.9
Puerto Rico	0.7
Nigeria (Ibadan)	0.1
South Africa (Cape Province, Bantu)	–
USA (Alameda, negro)	–

might be higher than that of African negroes. This may have contributed to our higher incidence. The marked increase in the incidence of testicular tumour in 1975 and 1976 is difficult to explain. Testicular tumour has been correlated with tumours of "affluence" such as colonic carcinoma (Berg *et al.*, 1973) in which the environment is suspect as a causative factor. Carcinoma of the colon is common in Jamaica, ranking sixth in order of incidence of malignant tumours in males (Persaud, 1976), contrasting with a very low incidence in Nigeria. While the incidence of testicular neoplasia is slightly higher in Jamaica, accounting for 0.3% of all male cancer (Persaud, 1976), it remains low in both countries.

A disturbing feature of this study is the delay in diagnosis, with the result that two-thirds of the patients had regional or distant metastases at the time of operation. One factor in late diagnosis may be the generally accepted view that these tumours are uncommon in negroes. We conclude that a greater awareness of the true incidence of these tumours in negroes might lead to earlier recognition.

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The Pattern of Spread and Treatment of Metastases in Testicular Seminoma

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Summary—The results of treatment of 199 patients referred to the Royal Marsden Hospital with testicular seminoma from 1963 to 1975 are described. Of 190 previously untreated patients 16 (8.4%) have died of seminoma, 3 (1.5%) of teratoma and 9 (4.9%) of intercurrent disease. Of 121 Stage I patients the only death was due to a second testicular tumour. In Stage II (54 patients) there was a significant association between length of history before orchiectomy and volume of abdominal node metastases. This was not, however, prognostically significant. Death from seminoma occurred in 6 out of 38 patients (15.8%) with nodal metastases ≤ 5 cm in diameter and 3 out of 16 patients (18.7%) with metastases >5 cm in diameter; 2 of 8 Stage III patients died of seminoma. Thus radiation controlled nodal metastases in more than 80% of Stage I, II and III patients. In Stage IV patients and patients referred with disease relapse, 12 out of 16 patients died of seminoma.

Chemotherapy experience is briefly reviewed. Cyclophosphamide as a single agent has produced a 50% response rate. There is no evidence to suggest a radiation-related increase in mortality from the group of long-term tumour-free survivors.

Testicular seminoma is characterised by its prompt and marked responsiveness to radiation. There is less information on the response of disseminated seminoma to chemotherapy, although it has been generally assumed that the radiosensitivity of the tumour is paralleled by a sensitivity to alkylating agents. The good survival figures achieved in seminoma are largely a reflection of the predominance at presentation of patients with early stage disease. Because of the high degree of sensitivity of seminomas to radiation and the fact that the majority of tumours occur in the most active and productive years, it is of particular importance to assess the shortcomings of current approaches to management in patients with metastatic disease so that steps can be taken to correct them.

Patients and Methods

Details on 199 patients with testicular seminoma referred to the Royal Marsden Hospital between 1963 and 1975 form the basis for this report; 190 were previously untreated and 9 had been treated elsewhere before referral.

Staging Methods

These included lymphography, intravenous urography, chest radiograph, liver function tests, bone and liver scans; ^{67}Gallium scans (Paterson *et al.*, 1976) were carried out in selected patients. Alphafetoprotein (AFP) and human chorionic gonadotrophin (HCG) are now measured routinely but were not done in most of the patients in this series. Laparotomy has been performed in a small number of carefully selected patients with bulky abdominal disease for accurate delineation of tumour. This will probably be rendered unnecessary since the whole body CT scanner now provides adequate detail for accurate radiotherapy planning.

Staging Classification

Stage I Lymphogram negative, no evidence of metastasis.

Stage II Positive lymphogram, no supradiaphragmatic nodal involvement or distant metastasis. Previous experience with testicular teratomas has shown a relationship between retroperitoneal nodal volume and radiocurability (Tyrrell and Peckham, 1976). To test this possibility in seminomas we have arbitrarily subdivided Stage II patients in the following way:

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A. ≤5 cm maximum diameter of abdominal node metastasis on lymphography, ultrasound scanning or intravenous urography.
B. >5 cm maximum diameter.

Stage III Infradiaphragmatic and supradiaphragmatic nodal metastases.

Stage IV Metastasis outside the lymphatic system (liver, lung, bone, etc.).

Radiotherapy

Details of radiotherapeutic techniques have been previously published (Peckham, 1976).

Stage I patients received a nodal dose of 3000 rad in 3 weeks (para-aortic and ipsilateral pelvis). The upper level of the field was D10/11 and the lower the obturator foramen. If orchidopexy or transcrotal surgery or interference had taken place, the ipsilateral inguinal nodes and scrotal sac were irradiated with shielding of the remaining testis.

Stage II patients received in addition 3000 rad to mediastinal and supraclavicular nodes. When bulky abdominal nodes were present great care was taken in more recent patients to localise tumour (including laparotomy if necessary). In a few cases tumour shrinkage was effected by chemotherapy before initiating irradiation. If renal irradiation was unavoidable a second phase employing lateral wedged fields was employed (Tyrrell *et al.*, 1977).

Stage III and IV patients were individualised. Essentially, in addition to chemotherapy an attempt was made to irradiate systematically all identifiable tumour.

Chemotherapy

When chemotherapy was indicated most patients (24 out of 35) received alkylating agents (Cyclophosphamide (19), Melphalan (1), Chlorambucil (4)). Six received Vinblastine, Actinomycin D and Methotrexate (VAM), 1 Mustine, Vinblastine, Procarbazine and Prednisone (MVPP) and 4 a range of drugs alone or in combination. Alkylating agent dosage varied, being either conventional low dose oral administration, conventional intravenous pulses of drug or, in a few patients, high dose (5 g) Cyclophosphamide with 24-hour forced intravenous hydration to protect the urothelium.

Histology

The histology has been reviewed by the Department of Histopathology, Royal Marsden Hospital. In more recent cases a newly developed immunocytochemical technique has been employed to examine sections for evidence of syncytial cells containing HCG (Heyderman and Neville, 1976).

Results

The stage distribution of previously untreated patients is summarised in Figure 1 and shows the predominance of Stage I (lymphogram negative) presentations. The length of history has been examined in relation to the size of abdominal node metastases (Stage IIA and IIB). Figure 2 summarises the results. The duration of history before presentation varies widely but the median values are significantly different ($P<0.05$).

Results of Treatment in Previously Untreated Patients

(A)

Figure 3 summarises the percentage cumulative

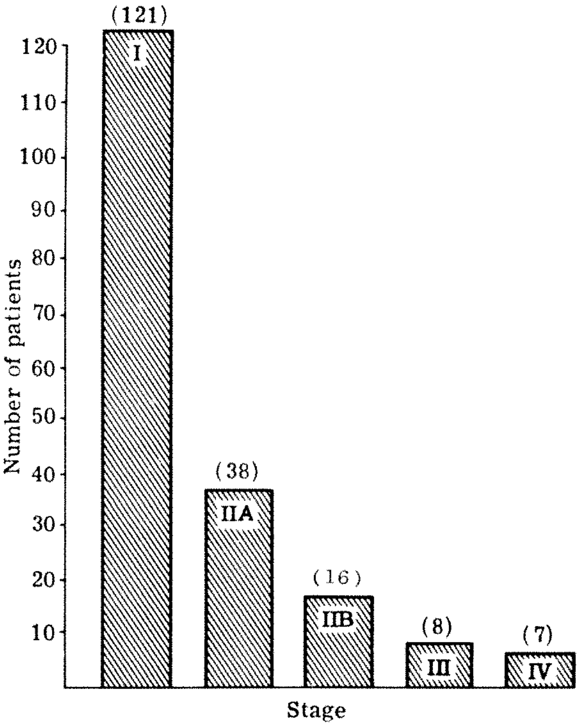

Fig. 1 Seminoma of testis (Royal Marsden Hospital, 1963-1975). Stage distribution at presentation of 190 previously untreated patients.

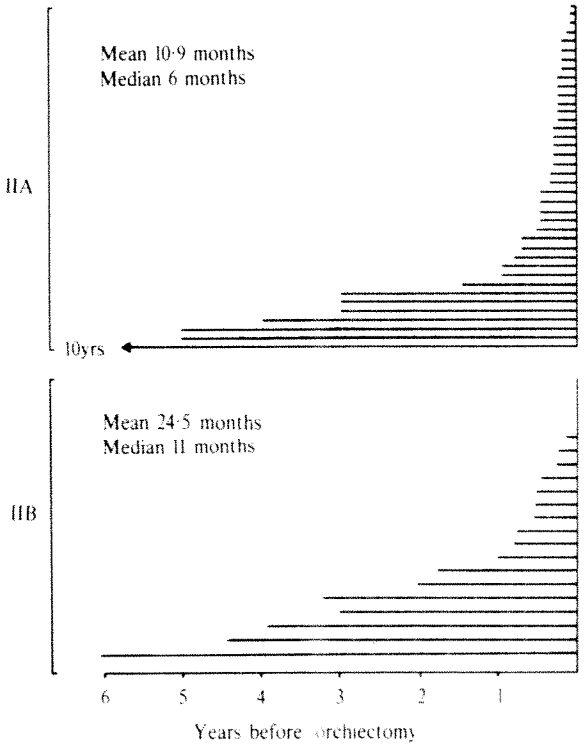

Fig. 2 Seminoma of testis (Royal Marsden Hospital, 1963-1975). Length of history in relation to volume of abdominal node metastases.

relapse following orchiectomy and initial therapy in Stage I, II and III patients; 80% of relapses occurred within 2 years of presentation but occasional late relapses up to 6 years are encountered.

Stage I There were 121 Stage I patients treated following orchiectomy with para-aortic and pelvic nodal irradiation on the assumption that a proportion harbour occult nodal micrometastasis.

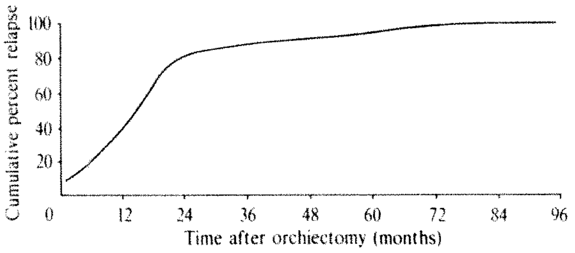

Fig. 3 Time to first relapse in testicular seminoma.

The results are shown in Table 1. Only 1 patient has died from seminoma and this was as a result of metastatic spread from a second seminoma subsequently developing in the contralateral testis. In this series 11 patients developed second tumours and this will form the basis of a separate report (Sokal *et al.*, 1978). Four of the Stage I patients relapsed, 3 developing supradiaphragmatic nodal metastases successfully treated by radiation. The fourth patient developed a slowly growing solitary pulmonary metastasis which was excised and he remains well 2 years later. In all, 13 patients were lost to follow-up. These were late losses to follow-up beyond the 2-year minimum observation period and since they were all in complete remission at their previous visit they were assumed not to have relapsed.

Stage IIA Of 38 patients in this group 6 have relapsed and all died of their tumour. Two of these patients relapsed initially in the scrotum and inguinal region which had not been irradiated in spite of locally advanced tumours.

Stage IIB Of 16 patients included in this category 4 relapsed and 3 died of seminoma. The fourth is alive with active disease.

Table 1 The Results of Treatment by Stage of 190 Previously Untreated Patients with Seminoma Testis (Royal Marsden Hospital 1963-1975)

	Total patients	*Lost to follow-up*	*Relapsed*	*Died of intercurrent disease*	*Died seminoma*	*Developed second tumour*
Stage I	121	13	4	4	1 (second tumour)	7
Stage IIA	38	1 (42 months)	6	4	6	0
Stage IIB	16	0	4	1	3	0
Stage III	8	1 (67 months)	$1/^{1}_{\text{NC}}$	0	2	2 (both died teratoma)
Stage IV	7	1 (9 months)	$0/^{4}_{\text{NC}}$	0	4	1 (died teratoma)

NC = Never controlled by therapy.

Stage III One of the 8 patients with Stage III disease relapsed and died. Two patients developed and died of teratomatous second tumours.

Stage IV Of 7 patients in this group only 1 is alive 3 years after initial treatment. One patient developed a second primary teratoma shortly after presentation and 1 had mixed tumour metastases (MTI), although the primary tumour was a pure seminoma. The other patients died of disseminated tumour uncontrolled by therapy.

(B)

Previously treated patients (Table 2).

Stage I Seven patients who were apparently Stage I at presentation were referred on relapse. Five died of seminoma and 1 developed a second testicular tumour, dying of metastases which were shown to be undifferentiated malignant teratoma at autopsy.

Stage II One of 2 patients in this group died of uncontrolled seminoma.

The pattern of relapse has been analysed and the sites of relapse are summarised in Figure 4.

The Results of Chemotherapy

In view of the infrequency of disseminated seminoma no systematic approach has been developed and over the years a wide variety of single agents and combinations has been employed. In most cases an alkylating agent was used initially and, in the event of failure to control the tumour, other chemotherapeutic agents were used, either alone or in combination.

Table 3 summarises the treatments employed and the tumour response as far as could be evaluated retrospectively. Seven patients achieved complete remission. Of 6 who did so with Cyclophosphamide, 4 were irradiated immediately after chemotherapy and remain well. The remaining 2 patients and the patient receiving Vinblastine, Actinomycin D and Methotrexate relapsed upon cessation of chemotherapy.

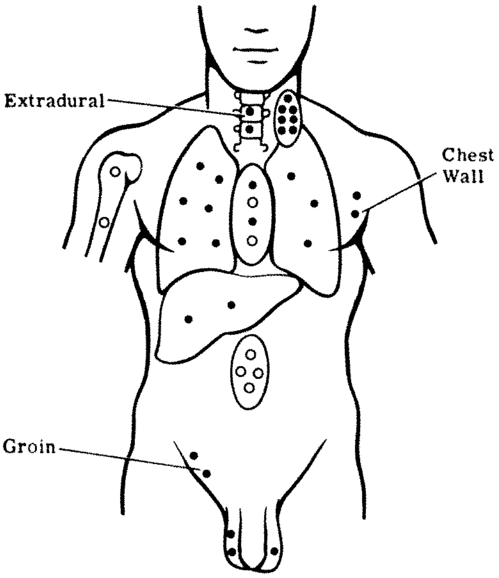

Fig. 4 Sites of first relapse in seminoma of testis, Stages, I, II, III.

Tumour Markers and Seminoma

Until the past 2 years HCG estimations have not been performed routinely on seminoma patients but only at the time of relapse or suspected disease activity. Twenty-eight patients had HCG estimated; it was elevated in the presence of active disease in 14 patients, 4 of whom had teratomatous second primary tumours. Only 4 patients found to have elevated HCG levels in the presence of active seminoma have responded well to treatment. In 1 patient it was elevated without signs of disease activity (Table 4).

Discussion

A progressive improvement in prognosis for testicular seminoma has been documented as radiotherapeutic facilities improved (Smithers, 1972). On the basis of the excellent overall survival figures, it has been a routine in this department for the past 15 years to irradiate the para-aortic and ipsilateral pelvic nodes after orchiectomy for

Table 2 Survival in Patients with Seminoma Testis Treated Elsewhere and Referred in Relapse (Royal Marsden Hospital 1963-1975)

Staging elsewhere	*Total patients*	*Lost to follow-up*	*Relapsed*	*Died of intercurrent disease*	*Died seminoma*	*Developed second tumour*
Stage I	7	0	7	0	5	1 and died
Stage II	2	0	2	0	1	0

Table 3

	No. of patients	*Complete remission*	*Partial remission*	*No remission*	*Not evaluable*
Cyclophosphamide	19	6*	4†	6	3
Melphelan	1	0	1	0	0
Chlorambucil	4	0	0	4	0
VAM	6	1	2	3	0
MVPP	1	0	0	1	0
ETC, MTX, VCR, Actinomycin D, CB, 154	4	0	0	4	0

* In all cases but 2, sites of bulky disease were irradiated immediately after achieving complete remission. Of complete responders 4 remain well with no signs of further relapse.
† Lasting 2 to 6 months.

negative lymphogram patients and to irradiate the mediastinal and supraclavicular fossae in addition in patients with positive lymphograms. Using the diagnostic criteria developed for interpretation of lymphography at this centre, 70% of patients with a seminoma have negative lymphograms. The proportion of patients within this group who have microscopic metastases is unknown but is likely to be relatively low (Maier *et al.*, 1968). There is no way in which the question can be readily resolved apart from desisting from irradiation in Stage I patients or directly sampling retroperitoneal nodes. The latter would be unjustifiable and the former probably unwise since, in the first place, the therapeutic approach is virtually unassociated with morbidity and, secondly, the monitoring of the untreated patient would be both time-consuming and inevitably involve investigations which are at the present time not repeated.

We are less concerned with the possibility that lymphograms interpreted as showing evidence of metastases are falsely positive since in lymphomas (Glees *et al.*, 1974), carcinoma of the bladder (Turner *et al.*, 1976) and cervix (Baker, 1976), the positive histological-radiological correlation has been high.

Table 4

Stage	*HCG elevated at relapse*	*HCG normal at relapse*	*Not done*	*Gynaecomastia* (normal HCG)*
I	5	1	4	2
II	7	5	4	3
III & IV	2	3	4	0
Total	14	9	12	5

* 4/5 patients are alive and well 4 to 9 years.

Overall in this series, 16 out of 190 patients have died of seminoma (8.4%), 3 of teratoma (1.5%) and 9 of intercurrent disease (4.9%). In Stage I, where irradiation is directed towards the elimination of presumed micrometastases in the retroperitoneal nodes, the only death in 121 patients was associated with reseeding from a second seminoma into the previously irradiated retroperitoneal area. The control rate can be assumed to be 100%.

In Stage II the ability of radiation to eradicate overt nodal metastases can be assessed. Overall, only 9 of 54 patients (16.7%) died of seminoma; 7 of these patients died of widespread extranodal metastases, non-responsive to therapy but with no signs of reactivation of their abdominal disease. The control rate in abdominal disease is thus approximately 83%. The tumour volume was associated with length of history but this appeared to exert no influence on prognosis, there being no significant difference between the 10-year survival of those patients with bulky disease (54%) and those with small volume disease (66%). In calculating these figures, deaths from intercurrent disease have not been subtracted from the total number and it has been assumed that the survival experience of those lost to follow-up is the same as those patients still being followed. Long-term follow-up is necessary in these patients as, although most relapses occur early in the history of the patient, seminoma is a tumour renowned for its tendency to later relapse (Friedman and Purkayastha, 1960; Strickland, 1965).

Of 8 Stage III patients, 2 died of seminoma. It may be concluded that nodal metastases can be controlled extremely well with radiation alone and that careful attention needs to be paid to accurate delineation of tumour and exclusion of teratomatous components histologically, by serum markers and immunocytochemical methods.

In a small number of patients with an abdominal mass, the true extent of tumour bulk has been delineated by clips placed in position at laparotomy. We are currently investigating the role of the whole-body CAT scanner in the localisation of intra-abdominal tumours in these patients prior to radiotherapy. We have failed to control nodal disease in only 3 patients, in 2 of whom failure was probably due to inaccurate assessment of the true extent of the tumour, resulting in a "geographical miss" in treatment. Of Stage I, II and III patients 9 out of 183 patients (4.9%) developed second tumours, 3 of which caused deaths in 2 cases from teratoma. Four of 7 Stage IV patients have died of seminoma and 2 of teratoma and 6 of 9 patients referred in relapse have died of seminoma and 1 of teratoma. This indicates that extension beyond the lymphatic system significantly reduces the chance of cure. Our limited chemotherapeutic experience shows a 50% response rate with Cyclophosphamide and this drug* should be regarded as the drug of choice in the absence of further information, particularly on drug combinations. Response rates of 50% have been reported elsewhere using alkylating agents alone (Du Priest and Fletcher, 1973) and Samuels *et al.* (1976) reported an 80% response rate with 4 out of 11 complete remissions using the Vinblastine-Bleomycin combination, although only 2 out of 11 patients were still alive. Since tumour regrowth tends to occur (Snyder *et al.*, 1964; Samuels *et al.*, 1976), it is our policy to irradiate identifiable tumour sites electively even if drug response is satisfactory.

In this series there have been 9 deaths from intercurrent disease in 183 patients with Stage I-III disease (Table 4). Of 54 Stage II patients where the mediastinum was electively irradiated there have been 5 deaths from intercurrent disease; 2 of these (3.7%) were due to cardiovascular disease. Bearing in mind that seminoma tends to occur a decade later than teratoma and our follow-up now extends to 14 years, these figures do not suggest that the treatment is associated with significant long-term morbidity.

The occasional slight elevation of chorionic gonadotrophin in apparent pure testicular seminoma is of interest. Recent work using an immunoperoxidase technique has demonstrated HCG-containing syncytial cells in some patients with testicular seminoma (Heyderman and Neville, 1976). The relationship of the presence of these cells to subsequent outcome is unknown at the present time.

Friedman and Pearlman (1970) have described a variant of seminoma called "seminoma with trophocarcinoma" which is associated with elevated HCG levels, which is more aggressive and more radio-resistant than pure seminoma and which they consider to be different clinically and histologically from combined tumours of the testis. Testicular tumours in which both seminoma and teratoma elements are identifiable account for approximately 14% of testicular tumours (Pugh, 1976). In our experience 2 of 21 seminoma patients (9%) dying of tumour had histological evidence of teratoma either at the time of relapse or autopsy. One explanation for this evolution is to assume that metastasis has occurred from a small undetected focus of teratoma present in the original tumour. However, the presence within 1 tumour of 2 histologically distinct components has not been satisfactorily explained in histogenetic terms. When found in combination with teratoma, the seminoma frequently forms discrete nodules of tumour, suggesting separate development (Dixon and Moore, 1953). It is conceivable that one element may precede the other in the process of tumour formation. If this is the case then it might be postulated that seminoma could evolve into teratoma and that this might explain the presence of histologically confirmed teratoma identified in relapse in some patients with an apparently pure seminoma primary.

In our experience we have not encountered a seminoma patient with an elevated serum alphafetoprotein level. Gynaecomastia in testicular teratoma tends to be associated with an elevated HCG level, but it is of interest in the present series that gynaecomastia was detected in 5 seminoma patients in the absence of an elevated HCG level and was of no prognostic significance in 4.

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* Since compiling this report we have employed high dose Melphalan in 2 patients with bulky tumour. Both have achieved good partial remissions after 1 dose of drug.

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Case Reports

An Unusual Trauma of the Glans Penis

Although trauma of the penile shaft is a rather common accidental occurrence, instances in which the glans has been traumatised by a dog-bite are extremely rare.

Case Report

An 18-year-old patient was admitted because of an unusual penile deformity. The glans and 1.5 cm of the distal penile shaft were hanging freely (Fig. 1). Between the glans and the penile shaft there was a dermal bridge like a cord, through which some vessels were passing for nourishment. The patient was able to urinate through an artificial hypospadiac meatus. On induced erection the glans and distal penile shaft showed no participation in this (Fig. 2). The patient was attacked by a dog when he was 8 years old in a remote village in Greece and because of urinary retention he had a hypospadiac meatus constructed. Recently the patient was seeking urological advice for surgical correction of his penile deformity which was causing him a great deal of emotional and psychological problems.

At operation, exploration of the dermal bridge was carried out, preserving carefully the nutritional vessels, and an end-to-end anastomosis of the glans and distal penile shaft was made. A Foley catheter was passed through the meatus up to the bladder. Initially the glans looked normal but on the seventh post-operative day it developed signs of ischaemic necrosis necessitating partial amputation.

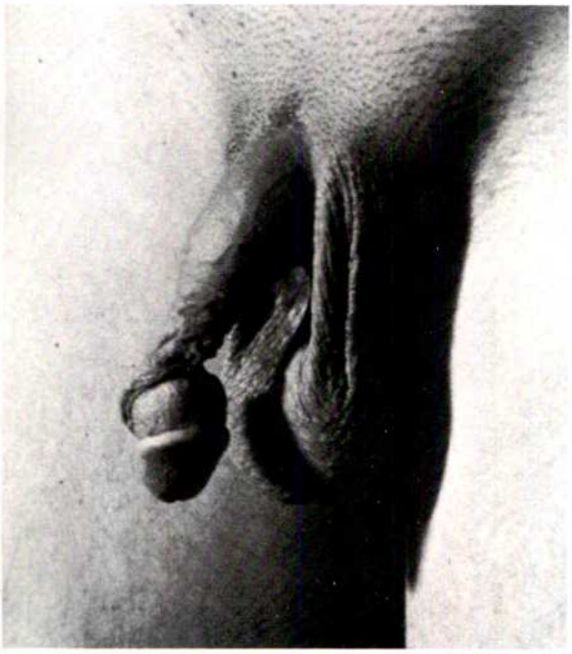

Fig. 1

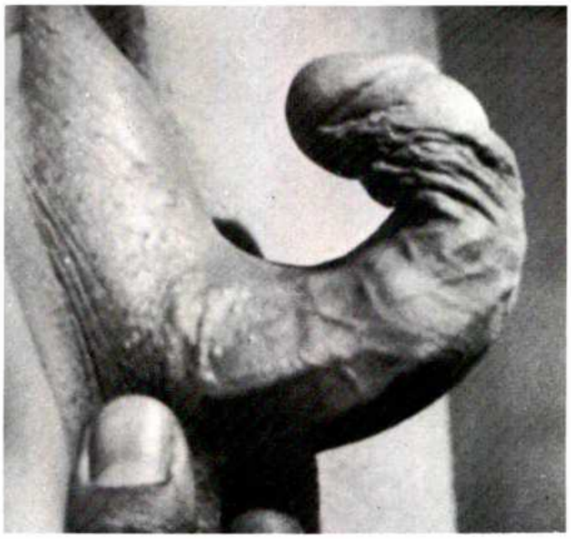

Fig. 2

Discussion

The glans may be injured accidentally or intentionally (Schulman, 1973).

Amputation of the glans penis has been successfully treated by re-anastomosis (Tuerch and Wir, 1971), but usually the glans has not survived. Marked oedema destroys the good results obtained after using microvascular techniques (Engelman *et al.*, 1974).

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Bilateral Diffuse Xanthogranulomatous Pyelonephritis

A rare case of diffuse bilateral xanthogranulomatous pyelonephritis with bilateral staghorn calculus is described. The pathology of the 2 kidneys supports the view that the disease is a complication of chronic suppurative pyelonephritis. Although this patient required bilateral nephrectomy, the need for early diagnosis and the possible role of conservative surgery are discussed.

Case Report

H.H., a 50-year-old Bedouin lady, was admitted in June 1976 with a 1-year history of malaise, intermittent bilateral loin pain and dysuria. Three years previously she had undergone left pyelolithotomy. She was pale, apyrexial and dehydrated with a tender right renal swelling. Urine contained pus and *E. coli*. A plain X-ray showed bilateral staghorn renal calculi and an ill-defined right renal mass. The patient left hospital against medical advice.

She was readmitted 5 months later with vomiting and loin pain. The right renal mass was unchanged but the left kidney was now palpable and tender. Investigations showed: Hb 5 g/dl; ESR 156 mm/h; blood urea 8.8 mmol/l; serum creatinine 246 μmol/l. An intravenous urogram revealed bilateral staghorn calculi with no excretion from the right kidney and markedly delayed excretion from the left. A left retrograde pyelogram displayed a dilated ureter but failed to show the pelvicaliceal system.

After antibiotic therapy, the replacement of fluid and the correction of the severe anaemia, the left kidney was explored. Perinephric vascular and inflammatory adhesions with pockets of suppuration prevented access to the renal hilum and although the staghorn calculus was removed by nephrotomies, nephrectomy proved unavoidable.

The patient was maintained on peritoneal dialysis. The urethral catheter drained thick pus from the pyelonephrotic right kidney and as the patient became more toxic a right nephrectomy was carried out. The patient has been maintained on haemodialysis and remains well.

Pathology

The left kidney weighed 300 g and contained a staghorn calculus. The capsule was adherent to the scarred cortex. The parenchyma was grey with yellow patches. Microscopically (Fig. 1a) there was a dense chronic inflammatory reaction with granular histiocytes, nodular patches of large foam cells containing PAS-positive material, and foci of calcification surrounded by granulomatous abscesses. Xanthomatous foci with inflammation, fibrosis and haemorrhage were also found in the perirenal tissues.

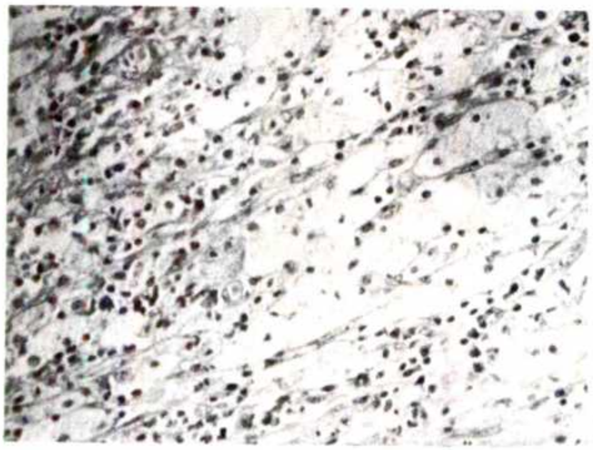

Fig. 1a Xanthogranulomatous pyelonephritis left kidney (H. and E. ×640).

The right kidney weighed 310 g and contained a staghorn calculus. The parenchyma was thin and yellow and the calices were dilated. Microscopically (Fig. 1b) the pattern was similar to that of the left kidney but the nodular patches of foam cells containing PAS-positive material and granular histiocytes were more discrete, and the fibrous reaction and calcification were more marked. The perirenal tissues were infiltrated by inflammatory cells without xanthogranuloma.

Bacteriology

Escherichia coli appeared to be the primary infecting organism, although pus taken from the urethral catheter contained *Proteus*, whereas pus taken from the kidneys was sterile.

Comment

This case is the second known report of bilateral xanthogranulomatous pyelonephritis, and the difference in the pathology of the 2 kidneys suggests different stages of the same disease.

Although the pathogenesis of the foam cell lesion in xanthogranulomatous pyelonephritis is

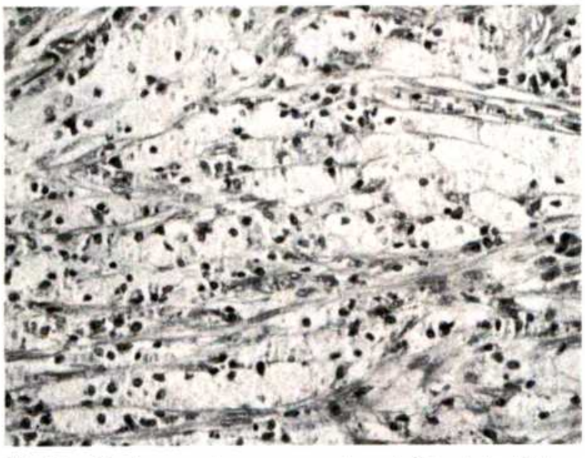

Fig. 1b Xanthogranulomatous pyelonephritis right kidney (H. and E. ×640).

unknown, the clinicopathological features are well defined. Two distinct patterns have emerged (Malek *et al.*, 1972). The focal type presents an avascular, localised renal mass with established angiographic features (Bissada *et al.*, 1976). The diffuse type is almost invariably associated with chronic, low grade suppuration, obstruction and calculi.

Gammill *et al.* (1975) experimentally produced post-inflammatory xanthogranulomas in rat kidneys by permanently ligating 1 ureter and injecting intravenously a suspension of *E. coli*. The lesions developed within 1 month and strikingly resembled those of human xanthogranulomatous pyelonephritis (Povysil, 1976).

In our case the more severely affected right kidney revealed much more fibroblastic activity around the xanthomatous foci and much less perirenal vascularity and suppuration than the left side. In Povysil's experiments PAS-staining glycoprotein appeared within the foam cells 1 month later than lipid, but before any significant collagen activity was noted. Although the origin of the lipid is still open to conjecture, it appears to be gradually replaced by PAS-staining glycoprotein and the xanthogranulomatous reaction gives way to renal fibrosis. The end stage of the disease is a small fibrosed kidney.

In all previously reported cases of the diffuse disease with staghorn calculus the kidney has been removed. Management should be conservative when bilateral involvement is suspected. Preoperative diagnosis of the diffuse form of the disease is extremely rare but it seems reasonable to assume that early relief of obstruction, together with appropriate antibiotic therapy, should achieve some renal recovery.

Acknowledgements

We are grateful to Dr A. R. Jaafar, Federal Director of Curative Medicine, for help during management of this case and to His Excellency The Minister of Health of the United Arab Emirates for permission to publish this report.

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British Journal of Urology (1979), **51**, 164

Obstructed Uropathy Treated by Chemotherapy

Cyotoxic chemotherapy has dramatically improved the prognosis of some patients with advanced malignant lymphoma. In the case described, this treatment alone was effective in relieving severe ureteric obstruction from para-aortic lymph node compression.

Case Report

A 57-year-old man presented with a 2-month history of increasing anorexia, malaise and left loin pain. On examination hard, moderately enlarged lymph nodes were palpable in the left axilla and in both inguinal regions, and there was an ill-defined central abdominal mass. Blood urea on admission was 36 mmol/l, creatinine 1.68 mmol/l, haemoglobin 10.4 g/dl and 24 h urine volume was 360 ml containing 18 mmol of urea. High dose urography demonstrated increased renal size and dilatation of the pelvi-caliceal systems. Bilateral retrograde pyelograms confirmed this and showed severe obstruction to the lower ureters (Fig.). A left inguinal lymph node was excised and histology was that of poorly differentiated lymphocytic lymphoma.

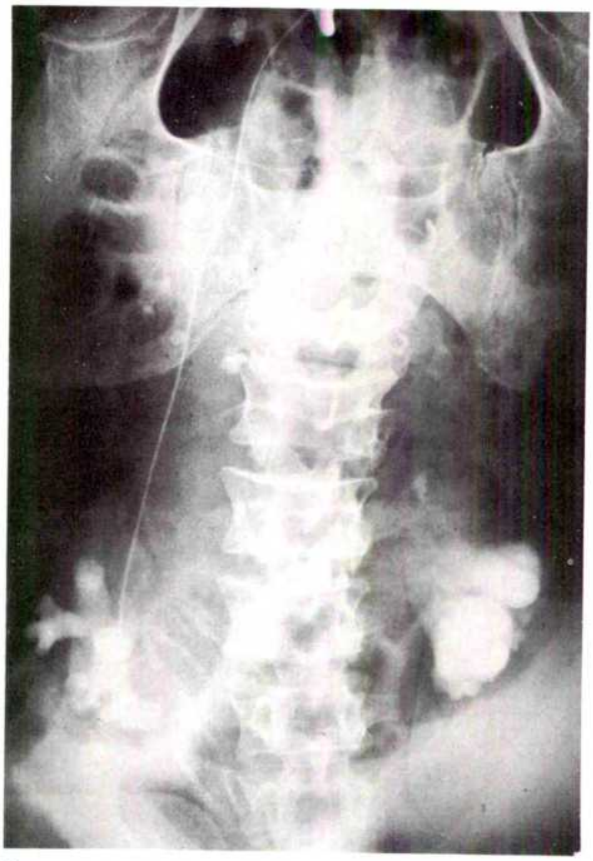

Fig.

The patient was then started on vincristine 2 mg i.v. stat., cyclophosphamide 330 mg daily, prednisolone 40 mg daily and allopurinol 10 mg b.d. The 24 h urine volume rose to 4.5 litres 3 days later, containing 773 mmol of urea. The serum creatinine returned to normal values within 6 days of the beginning of the treatment and remains stable at 2 months.

Comment

Partial ureteric obstruction occurs in at least 7% of patients with malignant lymphoma (Abeloff and Lenhart, 1974), but obstructive uropathy is unusual as the presenting feature. The rapid response to chemotherapy, as in this case, may obviate the need for direct surgical intervention.

Acknowledgement

We would like to thank Mr R. J. Barnard, Consultant Urologist, University Hospital of South Manchester, for his permission to present this case.

Reference

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A. Turner and D. E. Osborn, University Hospital of South Manchester, Manchester M20 8LR.

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British Association of Urological Surgeons: Annual Meeting

Bristol. 4-6 July 1979.

Further particulars from the Honorary Secretary, The British Association of Urological Surgeons, at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

International Conference on Urinary Calculi

Perth, Western Australia. 4-8 August 1979.

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Further information from: Assoc. Professor J. G. Brockis, International Conference on Urinary Calculi, University Department of Surgery, Royal Perth Hospital, Box X2213, G.P.O., Perth, Western Australia 6001.

Australasian Society of Nephrology. Annual Meeting

Perth, Western Australia. 8-11 August 1979.

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New York Hilton, New York. 13-17 May 1979.

Further particulars from: The Secretary AUA, 1120 N. Charles Street, Baltimore, Maryland 21201, USA.

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Further details from: The Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2. Telephone: 01-836 5361.

18th Congress of the International Society of Urology

Paris. 24-29 June 1979.

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European Association of Urology: Fourth Congress

Athens, Greece. 28-31 May 1980.

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Further particulars from: Congress President, c/o Hellenic Promotion Organisation, 36 Voukourestiou Street, Athens 136, Greece.

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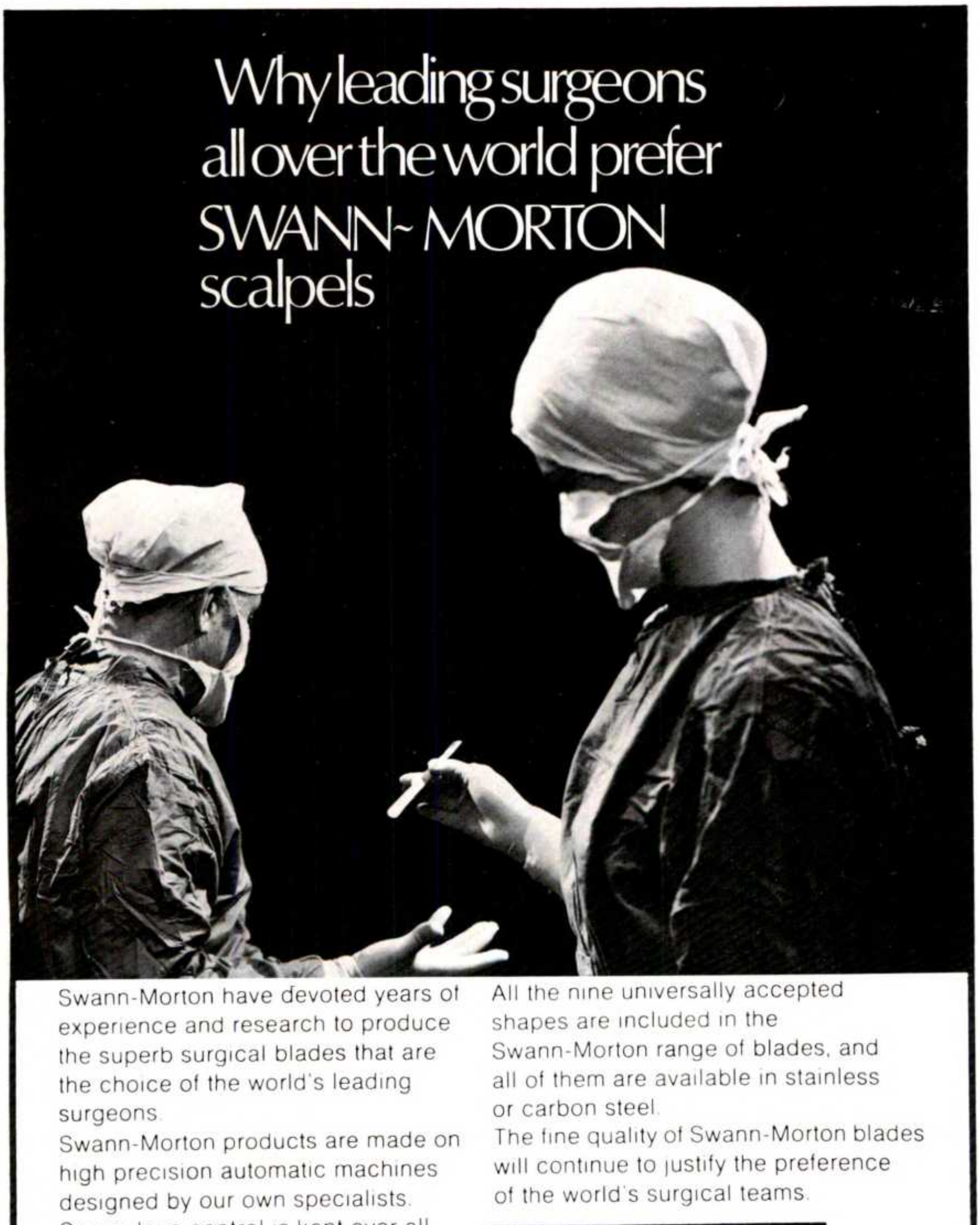
Venous blood						
Albumin	3.5-5.5	g/100 ml	10	0.1	35-55	g/l
Bicarbonate (total)	24-30	mEq/l	1	1	24-30	mmol/l
Bilirubin	0.1-0.8	mg/100 ml	17	0.059	2-14	μmol/l
Calcium	8.6-10.5	mg/100 ml	0.25	4	2.15-2.65	mmol/l
Chloride	100-107	mEq/l	1	1	100-107	mmol/l
Cholesterol	140-240	mg/100 ml	0.026	38.5	4.0-6.5	mmol/l
Creatinine	0.6-1.4	mg/100 ml	88	0.0114	55-125	μmol/l
Glucose	65-95	mg/100 ml	0.056	18	3.5-5.5	mmol/l
Iron	110-130	μg/100 ml	0.18	5.6	circa 20	μmol/l
Magnesium	1.4-1.8	mEq/l	0.5	2	0.70-0.90	mmol/l
Phosphate	2.5-4.5	mg/100 ml	0.32	3.1	0.8-1.4	mmol/l
Potassium	3.8-5.2	mEq/l	1	1	3.8-5.2	mmol/l
Protein (total)	6.5-8.0	g/100 ml	10	0.1	65-80	g/l
P.B.I.	3.75-7.5	μg/100 ml	79	0.0127	300-600	nmol/l
IgG	500-1600	mg/100 ml	0.01	100	5.0-16.0	g/l
IgA	125-425	mg/100 ml	0.01	100	1.25-4.25	g/l
IgM	50-180	mg/100 ml	0.01	100	0.5-1.8	g/l
Sodium	136-149	mEq/l	1	1	136-149	mmol/l
Transferrin	150-300	mg/100 ml	0.01	100	1.5-3.0	g/l
Triglyceride	60-140	mg/100 ml	0.0113	88.5	M2.0 P<1.5	mmol/l
Uric acid	2-7	mg/100 ml	0.06	16.7	0.1-0.4	mmol/l
Urea	15-40	mg/100 ml	0.17	6.0	2.5-6.5	mmol/l
Arterial blood						
Base excess	−3-+3	mEq/l	1	1	−3-+3	mmol/l
PCO_2	32-46	mmHg	0.135	7.5	4.5-6.0	kPa
PO_2	80-100	mmHg	0.133	7.5	10.5-13.5	kPa
Urine outputs/24 h						
Calcium	200	mg	0.025	40	5	mmol
Creatinine	1-2	g	8.8	0.113	9-18	mmol
5HIAA	3-17	mg	5.23	0.19	16-90	μmol
Inorganic P.	1000	mg	0.032	31	30	mmol
Magnesium	100	mg	0.041	24	4.2	mmol
Potassium	70	mEq	1	1	70	mmol
Protein	<0.05	g	1	1	<0.05	g
Sodium	200	mEq	1	1	200	mmol
Urea	25	g	17	0.06	400	mmol
Uric acid	500	mg	0.006	167	3.0	mmol
VMA	<7	mg	5.05	0.2	<35	μmol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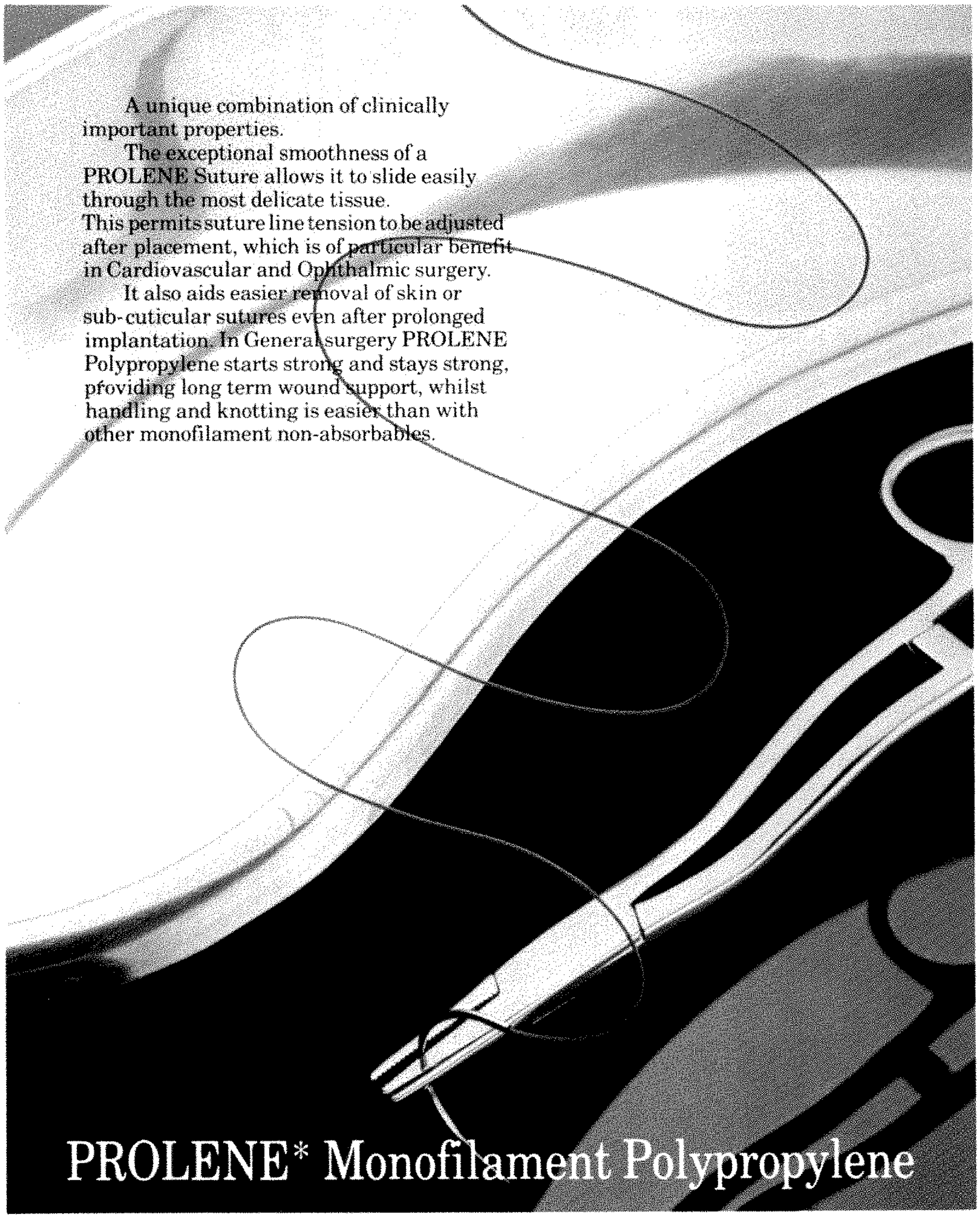

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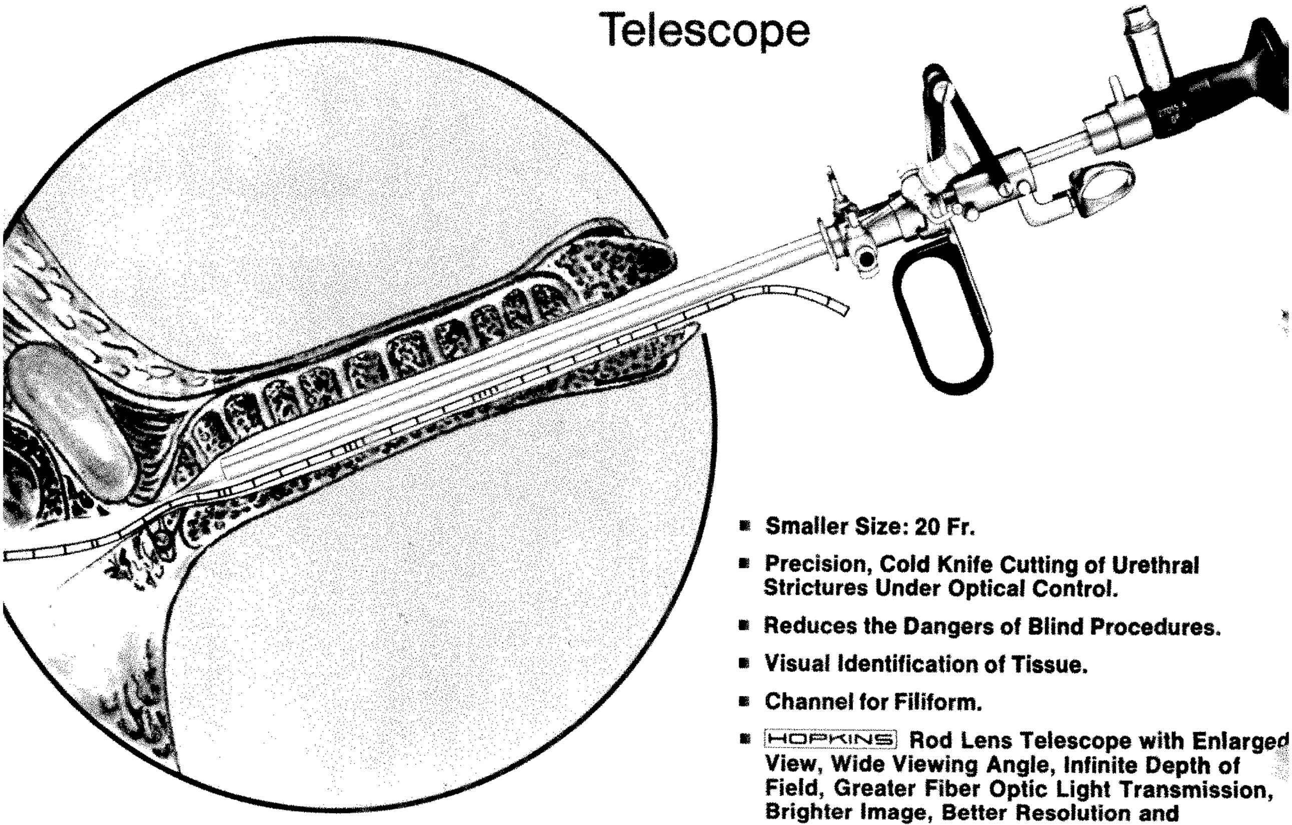

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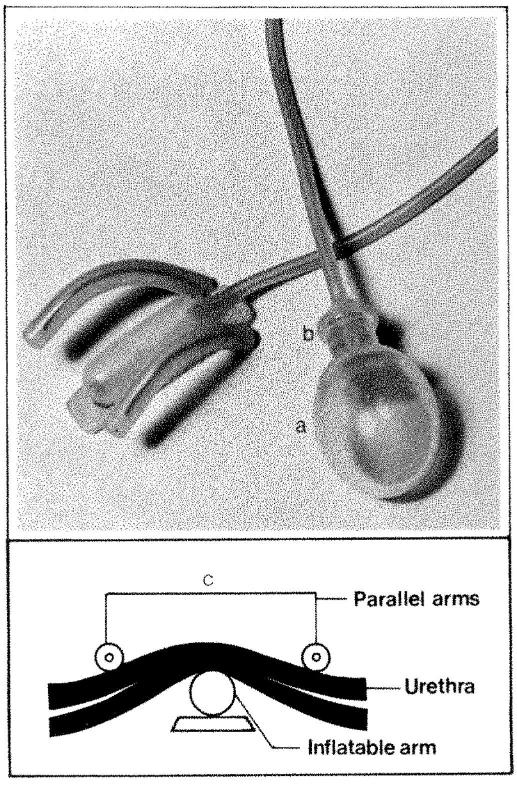

a) reservoir bulb and valve are situated in the scrotum squeeze to occlude urethra

b) squeeze to release urethra

c) parallel arms and inflatable arm fit over and under urethra

A film and further information is available from

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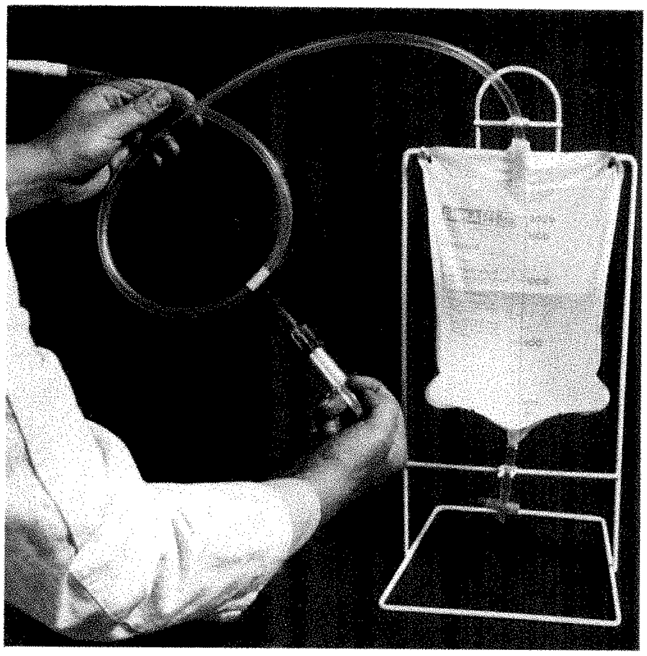

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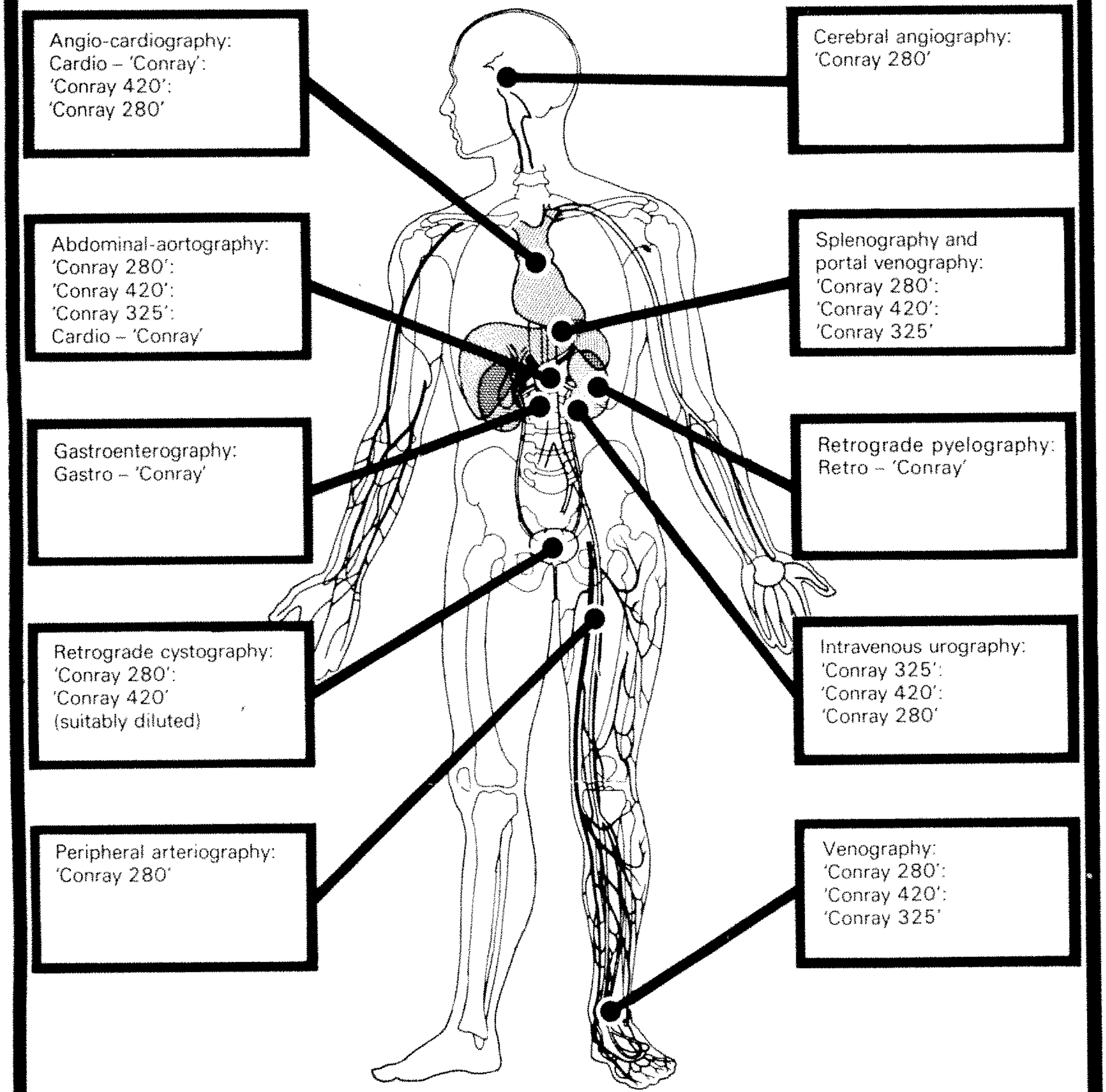

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'Ullo,
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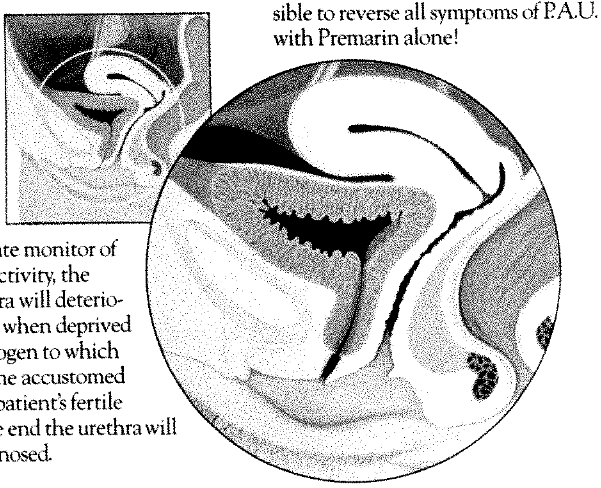
WINTHROP

The Diagnosis and Treatment of P.A.U.

Post-menopausal Atrophic Urethritis

Older women presenting with frequency, urgency and painful micturition often describe their condition as 'cystitis.' There can hardly be a woman in existence who has not suffered the transient discomfort of a 'simple cystitis' at some time in her early life, but as she reaches middle age, although the symptoms may appear to her as the same, the cause, particularly in the absence of infection, may be atrophic changes in the distal urethra responding to hormonal disparities of the menopause.[1]

Untreated, these atrophic changes can be devastating and demoralising in their effect.[2]



A delicate monitor of oestrogen activity, the distal urethra will deteriorate rapidly when deprived of the oestrogen to which it has become accustomed during the patient's fertile years. In the end the urethra will become stenosed.

Treating P.A.U. with Premarin*
Treatment with Premarin 0.625mg tablets can effect a rapid and complete elimination of symptoms.[3]

1. Oestrogen deprivation can be confirmed by vaginal cytology or assumed in the presence of vaginal atrophy or dryness, or other symptoms of oestrogen lack.

2. Low-dose Premarin (0.625mg) administered cyclically – 21 days on, 7 days off – for 3 months. Urethral epithelium is remarkably sensitive to oestrogens and so will respond to this low dose.

3. Frank urinary tract infection should of course be treated with appropriate antibiotics or urinary anti-infectives.

4. If treatment is instigated in the early stages of this disorder – for instance within the first six/twelve months of symptoms – it may be possible to reverse all symptoms of P.A.U. with Premarin alone!

However in patients with a longer history of frequency and urgency, if oestrogen therapy does not effect a rapid and complete elimination of symptoms then the possibility of a secondary urethral stenosis should be considered.

References:
1. Willington, F. L. The Practitioner. 220, 739, 1978.
2. Smith, P. J. B., Ayerst Medical Library Vol. 2, No 2, 1978.
3. Smith, P. J. B., The Practitioner, 218, 97, 1977.

PREMARIN
(conjugated oestrogens)

Premarin tablets

Uses
Menopausal and post-menopausal oestrogen replacement therapy and allied disorders such as post-menopausal osteoporosis, atrophic vaginitis and post-menopausal atrophic urethritis.

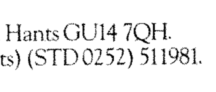
Dosage and Administration
Menopausal and post-menopausal oestrogen deficiency: Premarin 0.625–1.25mg daily is the usual starting dose. Cyclic administration is recommended (three weeks' dosage followed by one week's rest). For maintenance, the lowest effective dose should be used. It is recommended that a physical examination, including endometrial assessment, whenever possible be performed at the time of the initial examination, and the endometrium assessed regularly thereafter at 6–12 month intervals. Break through bleeding is an indication for further investigation.

Contra-Indications: Uterine myomatosis. Endometriosis. Cancer of the breast and uterus. Active hepatic, renal and severe cardiac disease. Undiagnosed genital bleeding. Diabetes. Thyrotoxicosis. Pregnancy. Personal history of thrombosis.

Precautions
In the female – prolonged use of unopposed oestrogen may increase the risk of endometrial carcinoma.

Side Effects
Premarin is unlikely to cause gastro-intestinal symptoms, headaches, breast tenderness, salt and water retention which can occur with other forms of oestrogen therapy.

Product licence numbers
Premarin Tablets 0.625mg. PL 0607/5000.
21 tablet pack £0.80.
Premarin Tablets 1.25mg. PL 0607/5001.
21 tablet pack £1.30.
Premarin Tablets 2.5mg. PL0607/0002.
30 tablets £2.40.



Ayerst International

Full prescribing information:
Ayerst Laboratories Limited,
Invincible Road, Farnborough, Hants GU14 7QH.
Telephone: Farnborough (Hants) (STD 0252) 511981.

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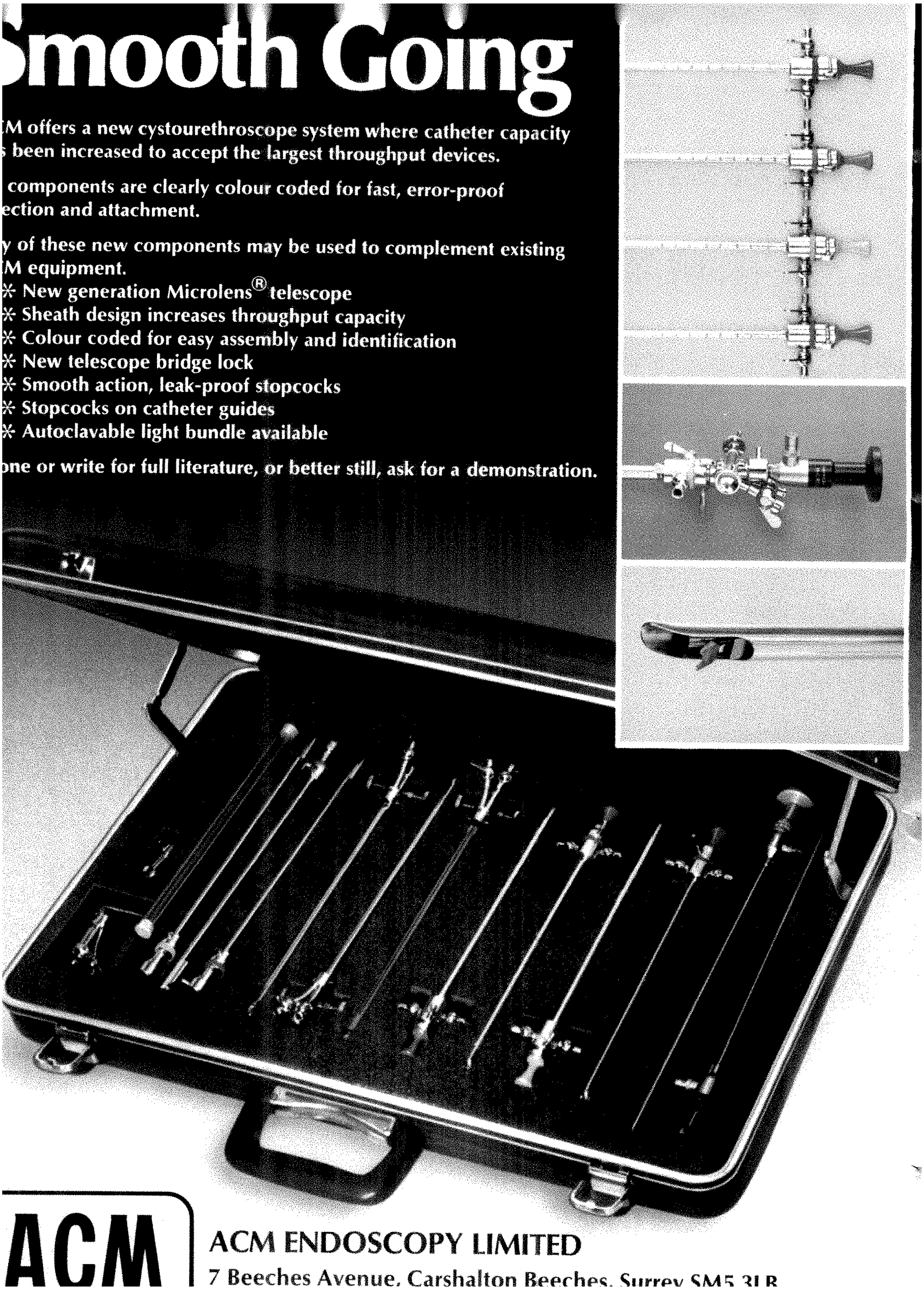

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Lepetit

A new approach to the problem of treatment of oestrogen-resistant carcinoma of the prostate.

ESTRACYT*

estramustine phosphate

A unique compound

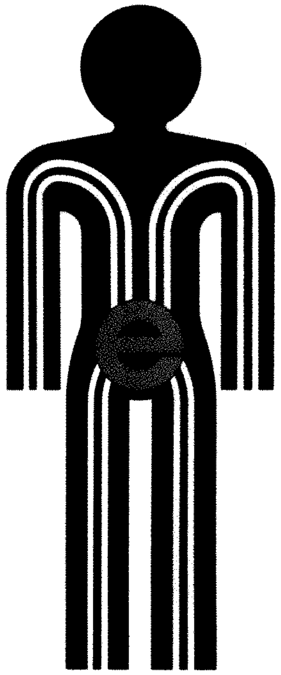
Estramustine phosphate (Estracyt) is a chemical compound of normustine and oestradiol. It utilises the concept of oestrogen as a carrier of the inert cytotoxic agent to the target tissue (with a high affinity for oestrogens) where cleavage of the molecule releases active normustine.

With a unique action

Estracyt appears to have specific affinity for, and effect on, prostate tissue but to have only weak systemic cytotoxic effects; thus long-term administration can be tolerated.

With unique results

In oestrogen-resistant carcinoma of the prostate, published results of treatment of over 500 patients with Estracyt relate to 80% with Stage IV disease and 20% Stage III. They show that SUBJECTIVE response to treatment, seen in 40% to 65% of oestrogen-resistant patients,[1,2] usually occurs within 14 days, relief of pain being the most obvious benefit. OBJECTIVE responses were seen in 19%–48% of patients with advanced disease.[3,4]



Indications. Carcinoma of the prostate, especially in cases unresponsive to, or relapsing after conventional oestrogen therapy or orchidectomy.
Dosage and Administration. The adult dose ranges from 1 to 10 capsules a day by mouth, with meals. Standard starting dose 4 capsules a day with later adjustment according to response. One to 2 capsules a day may be adequate for maintenance therapy.
Precautions. Caution in administration to patients with moderate to severe bone marrow depression.
Adverse Reactions. Commonly transient nausea, occasionally vomiting and rarely diarrhoea, gynaecomastia, angina, rash and/or fever, transient disturbance of liver function.
Contraindications. Peptic ulceration, severe liver disease or severe cardiac disease. Children.
Pharmaceutical Precautions. Store in cold place (2°C to 8°C).
Package Quantities. Bottles of 100 capsules.
P. L. No. 0458/0016
P. A. No. 115/3/1

Lundbeck

Further information and data sheet are available from Lundbeck Limited, Lundbeck House, Hastings Street, Luton Beds. LU1 5BE

References
1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., 49, 73-79. 2. Mayer. E.J. Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, 32, 114-119. 3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., 111: 231-238. 4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

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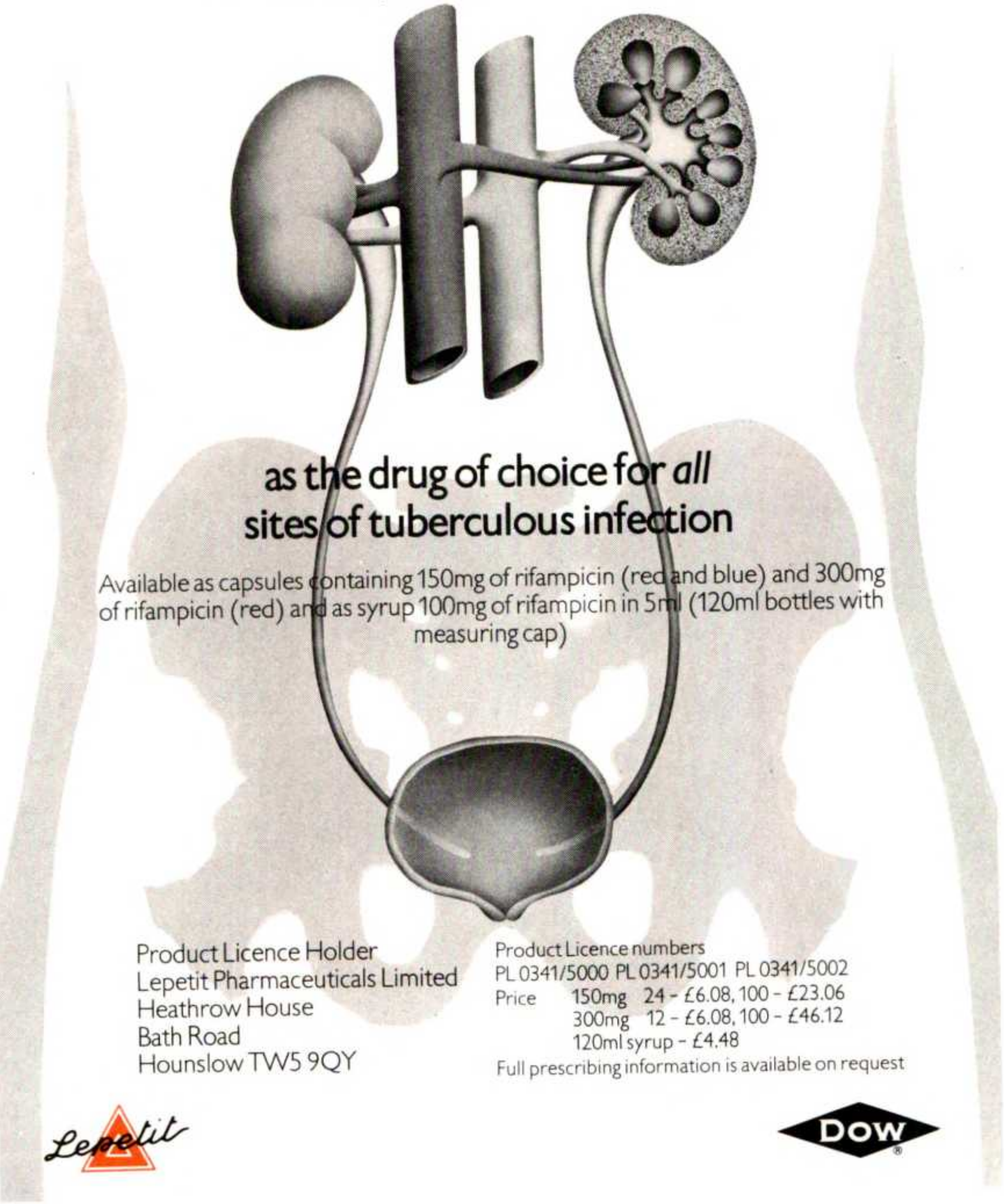

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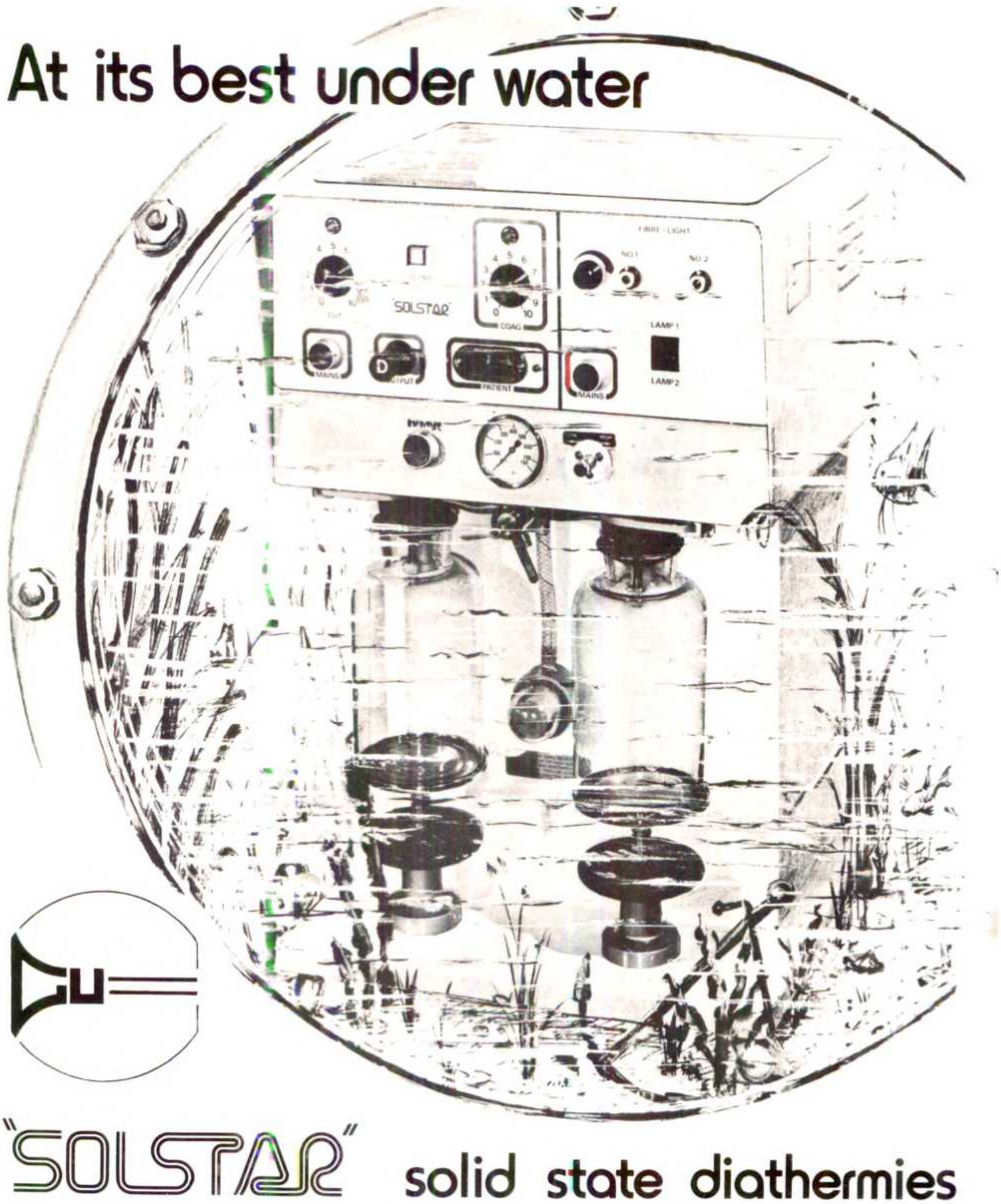

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Trademark

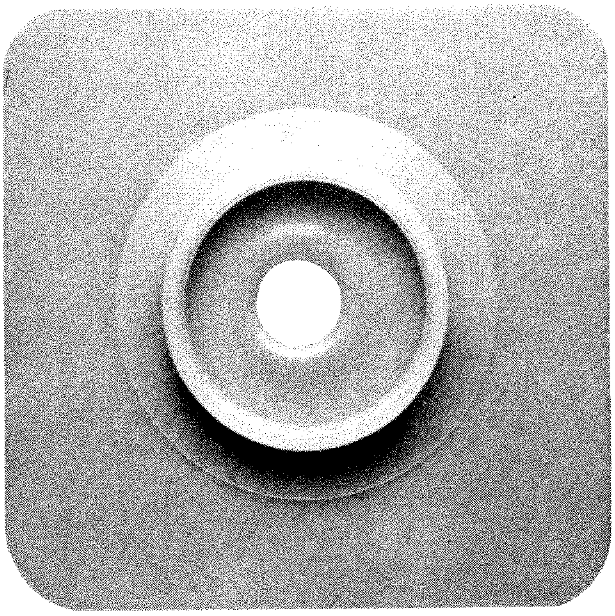
Surgicare™ System 2 saves the daily trauma of peeling off adhesive bags often resulting in irritation, soreness and discomfort.
The Stomahesive™ with Flange can be left on the skin undisturbed for several days whilst pouches are replaced as often as necessary... so simply.

Kinder to the skin

Stomahesive™ with Flange may be used by patients who have experienced sensitivity reactions when using ordinary adhesives and karaya or where perspiration under the adhesive is a regular source of irritation and discomfort

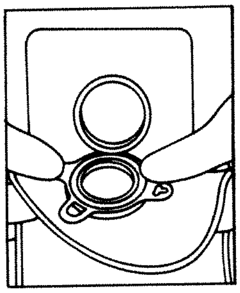
Unequalled comfort

The Stomahesive™ base will mould to irregular contours of the skin and is so easy to apply without wrinkling. Comfort is derived not only from the feel of Stomahesive™ against the skin but from the confidence that the appliance will be secure and leak free irrespective of the condition of the skin.

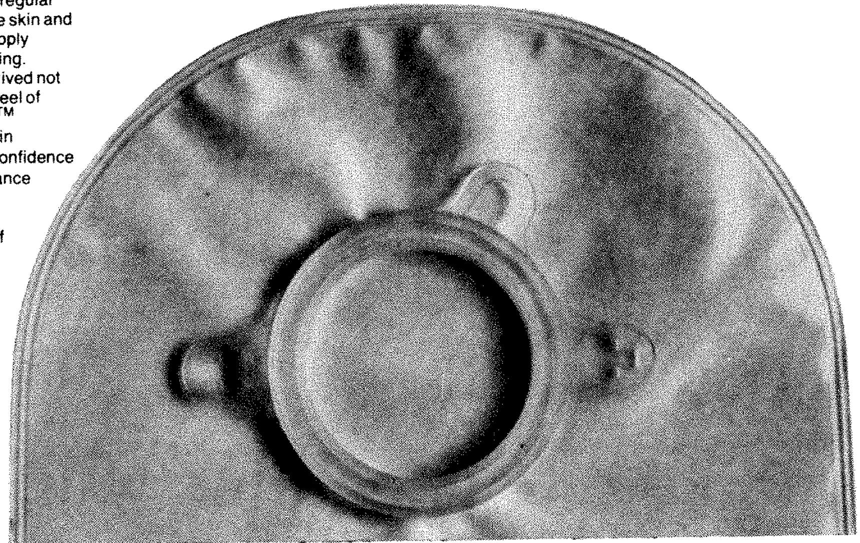


Avoids adhesive trauma

With the Stomahesive™ flange remaining undisturbed, pouches may be removed and replaced as necessary.



The colostomist, for example, may change pouches several times a day without the need to disturb the Stomahesive™ base and its flange.



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NEOPLATIN*

PRESENTATION

NEOPLATIN INJECTION : each vial contains 10 mg cisplatin (Cis-diamminedichloroplatinum).

USES

Cisplatin is indicated as palliative therapy to be employed in addition to other modalities, or in established combination therapy with other approved chemotherapeutic agents in the management of neoplastic diseases, especially :

Metastatic Testicular Tumours – in patients who have already received appropriate surgical and/or radiotherapeutic procedures. The combination of cisplatin, bleomycin and vinblastine has been reported to be highly effective. Other combinations have also been reported to be active.

Metastatic Ovarian Tumours – as secondary therapy in patients refractory to standard chemotherapy.

DOSAGE AND ADMINISTRATION

The recommended dose of cisplatin in adults and children as single-agent therapy is 50 to 75 mg/m^2 as a single i.v. dose every 3 to 4 weeks, or 15 to 20 mg/m^2 i.v. daily for 5 days every 3 to 4 weeks. Pre-treatment hydration with 1 to 2 litres of fluid infused for 8 to 12 hours prior to a cisplatin dose is recommended. Reconstitute vial contents with 10 ml of sterile water for Injection EP. The drug is then diluted in 2 litres of 5% dextrose in either 1/2 or 1/3 normal saline, (to which 37.5 g of mannitol may be added) and infused over a 6-8 hour period. Adequate hydration and urinary output must be maintained during the following 24 hours.

A repeat course of cisplatin should not be given until the serum creatinine is below 1.5 mg/100 ml (130 μmol/l) and/or the blood urea below 55 mg/100 ml (9 mmol/l). A repeat course should not be given until circulating blood elements are at an acceptable level (platelets 100,000/mm^3, WBC 4,000/mm^3). Subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits. When employed in combination with other antitumour drugs, the dose of cisplatin should be adjusted appropriately.

CONTRA-INDICATIONS, WARNINGS, ETC.

Cisplatin induces nephrotoxicity, myelosuppression and ototoxicity which may be additive to pre-existing dysfunctions. Consequently, the use of cisplatin in patients with hearing or renal impairment or depressed bone marrow function may be associated with increased toxicities. Such conditions represent relative contra-indications.

Cisplatin is contra-indicated in patients with a history of hypersensitivity to cisplatin or other platinum-containing compounds.

WARNINGS

Cisplatin produces cumulative nephrotoxicity. The serum creatinine, BUN and creatinine clearance should be measured prior to initiating therapy, and prior to each subsequent course.

Anaphylactic-like reactions to cisplatin have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to cisplatin, and have been alleviated by administration of adrenaline, steroids and antihistamines.

Safe use in pregnancy has not been established. This product should not normally be administered to patients who are pregnant or to mothers who are breast feeding. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. Although carcinogenicity and teratogenicity have not been established, compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

The influence of cisplatin on human reproduction has not been determined. Cisplatin therapy might have an antifertility effect.

Precautions

Cisplatin should be administered by individuals experienced in the use of antineoplastic therapy.

Since renal toxicity is cumulative, measurements of BUN, serum creatinine and creatinine clearance should be performed prior to initiating therapy and prior to each subsequent dose. At the recommended dosage, cisplatin should not be given more frequently than once every 3 to 4 weeks. (See Adverse Reactions)

Since ototoxicity of cisplatin is cumulative, audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug. (See Adverse Reactions)

Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurological examination should also be performed regularly. (See Adverse Reactions)

ADVERSE REACTIONS

Nephrotoxicity

Dose-related and cumulative renal insufficiency is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28 to 36% of patients treated with a single dose of 50 mg/m^2. It is first noted during the second week after a dose and is manifested by elevations in BUN and serum creatinine, serum uric acid and/or a decrease in creatinine clearance.

Renal toxicity, becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given.

Renal function impairment has been associated with renal tubular damage. The administration of cisplatin using a 6-8 hour infusion with intravenous hydration and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilisation of these procedures.

Ototoxicity

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4,000 to 8,000 Hz).

Decreased ability to hear normal conversational tones may occur occasionally. Ototoxic effects may be more severe in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. It is unclear whether cisplatin-induced ototoxicity is reversible. Careful monitoring of audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin.

Haematological

Myelosuppression occurs in 25 to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leucocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leucopenia and thrombocytopenia are more pronounced at higher doses (50 mg/m^2). Anaemia (decrease in haemoglobin level by 2 g/100 ml blood) occurs at approximately the same frequency and with the same timing as leucopenia and thrombocytopenia.

Gastrointestinal

Marked nausea and vomiting occur in almost all patients treated with cisplatin, and are occasionally so severe that the drug must be discontinued. Nausea and vomiting usually begin within one to four hours after treatment and last up to 24 hours. Various degrees of nausea and anorexia may persist for up to one week after treatment.

OTHER TOXICITIES

Hyperuricaemia

Hyperuricaemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricaemia effectively reduces uric acid levels.

Neurotoxicity

Neurotoxicity, usually characterised by peripheral neuropathies, has occurred in some patients. Loss of taste and seizures have also been reported. Neuropathies resulting from cisplatin treatment may occur after prolonged therapy (4 to 7 months), however, neurological symptoms have been reported to occur after a single dose.

Cisplatin therapy should be discontinued when the symptoms are first observed. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients.

Anaphylactic-like Reactions

Anaphylactic-like reactions, possibly secondary to cisplatin therapy, have been occasionally reported in patients previously exposed to cisplatin. The reactions consist of facial oedema, wheezing, tachycardia and hypotension within a few minutes of drug administration. All reactions may be controlled by intravenous adrenaline, corticosteroids or antihistamines. Patients receiving cisplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Other toxicities reported to occur infrequently are cardiac abnormalities, anorexia and elevated SGOT.

PHARMACEUTICAL PRECAUTIONS

NEOPLATIN INJECTION must be stored in a refrigerator (2°C to 8°C).

EXPIRY DATE

24 months from date of manufacture.

Preparation of Intravenous Solution

Dissolve NEOPLATIN with 10 ml of sterile water for injection. Each ml of the resulting clear, colourless solution will contain 1 mg cisplatin.

The drug is diluted in 2 litres of 5% dextrose in 1/2 or 1/3 normal saline (to which 37.5 g of mannitol may be added) and given by i.v. infusion over a 6 to 8 hour period.

The reconstituted solution should be protected from light, kept at room temperature and is stable for 20 hours. Refrigeration will result in precipitation.

LEGAL CATEGORY

POM

NEOPLATIN is available only on prescription and supplied to centres with experience in the chemotherapy of malignant disease.

PACKAGE QUANTITIES

NEOPLATIN INJECTION is packed in cartons of 10 vials, each vial containing 10 mg lyophilised cis-diamminedichloroplatinum.

FURTHER INFORMATION

Cisplatin has biochemical properties similar to that of bifunctional alkylating agents producing interstrand and intrastrand crosslinks in DNA. It is apparently cell-cycle non-specific. Following a single i.v. dose, cisplatin concentrates in liver, kidneys and large and small intestines in animals and humans. Cisplatin apparently has poor penetration into the CNS.

Plasma levels of radioactivity decay in a biphasic manner after an i.v. bolus dose of radioactive cisplatin to patients. The initial plasma half-life is 25 to 49 minutes, and the post-distribution plasma half-life is 58 to 73 hours. During the post-distribution phase, greater than 90% of the radioactivity in the blood is protein bound. Cisplatin is excreted primarily in the urine. However, urinary excretion is incomplete with only 27 to 43% of the radioactivity being excreted within the first 5 days post-dose in human beings. There are insufficient data to determine whether biliary or intestinal excretion occurs.

BASIC N.H.S. COST 10mg vial £10.75

PRODUCT LICENCE NUMBER 0125/0109

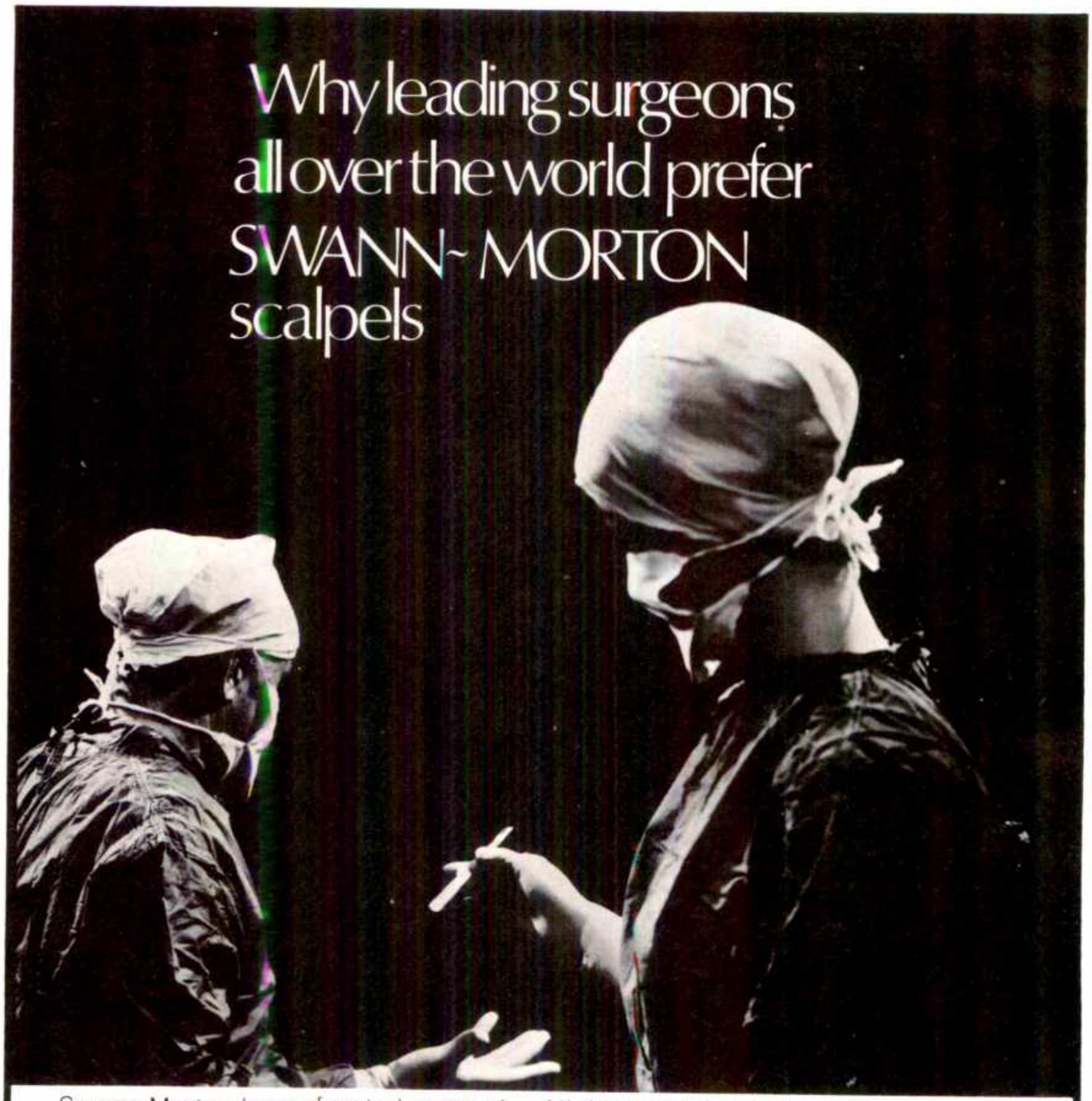
DATE OF PREPARATION

January 1979

NAME AND ADDRESS

MEAD JOHNSON LABORATORIES
Division of Bristol-Myers Company Limited,
Station Road, Langley, Slough SL3 6EB. (Tel. No. Slough 44266)

*Trade Mark Authorised User Bristol-Myers Company Limited



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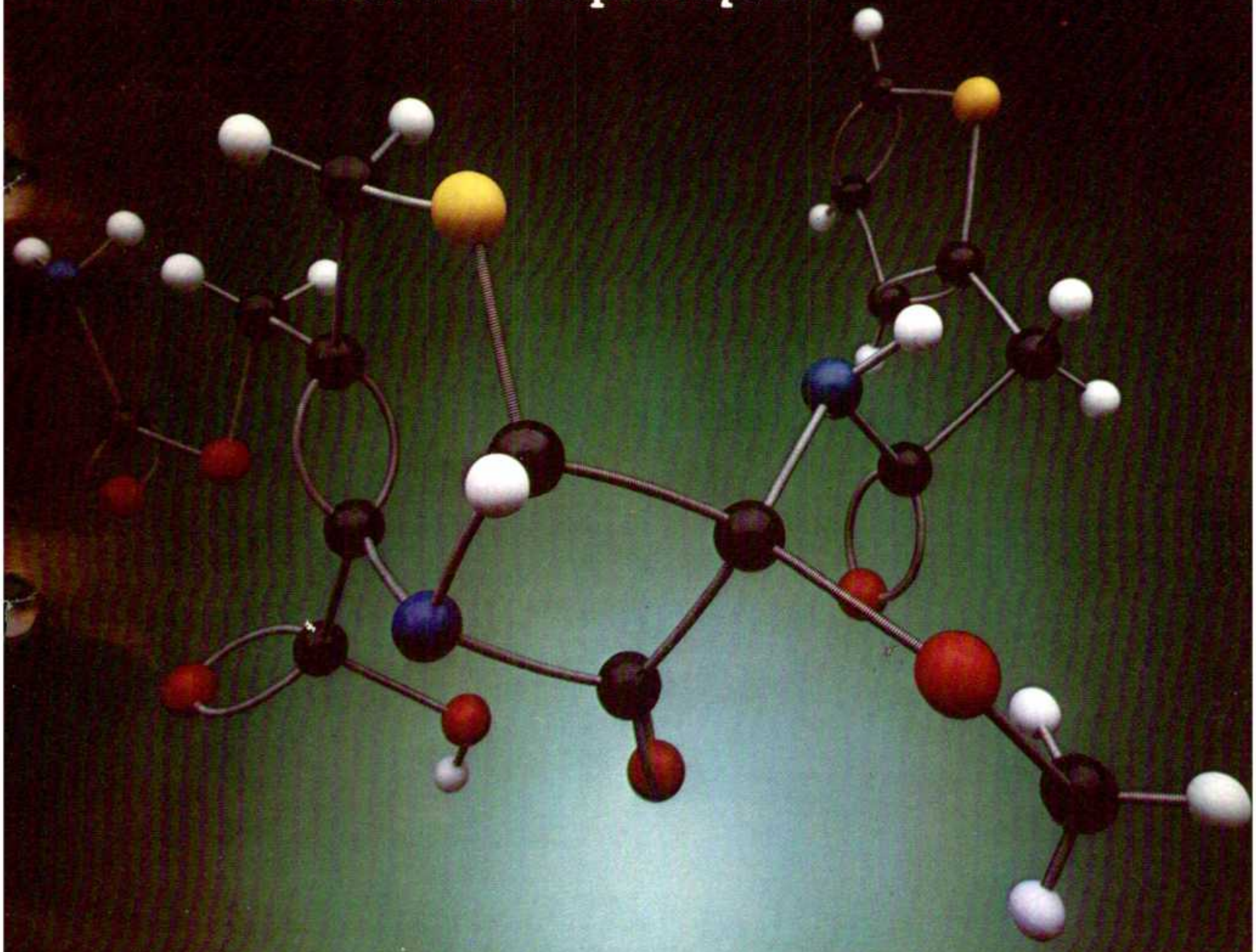
MSD announces
the discovery of

Mefoxin®

Cefoxitin sodium, MSD

INJECTION

First of the cephamycins

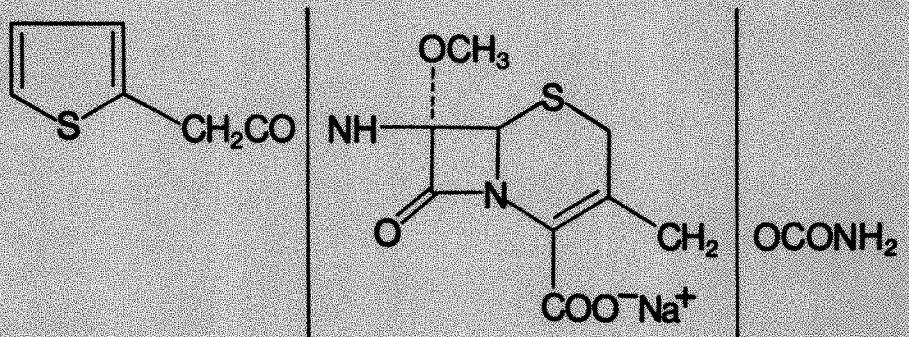


A new class of antibiotics

'Mefoxin' is derived from cephamycin C, a naturally occurring antibiotic substance produced by *Streptomyces lactamdurans*. This naturally occurring antibiotic has been modified in the MSD Research Laboratories to enhance its therapeutic usefulness.

Prescribing information overleaf

'Mefoxin' has a unique molecular structure offering outstanding clinical benefits and a specific clinical profile.



Thienylacetyl side-chain:

enhances activity against Gram-positive pathogens

Cephamycin nucleus:

provides bactericidal activity against a wide range of pathogens, Gram-negative in particular. 7α-methoxy group protects against β-lactamase degradation

Carbamoyloxy side-chain:

protects antibiotic from being metabolised

▼Prescribing information

Indications

'Mefoxin' is a broad-spectrum bactericidal antibiotic indicated for the treatment of infections caused by susceptible strains of Gram-positive and Gram-negative pathogens both aerobic and anaerobic.

'Mefoxin' has been clinically effective not only in infections due to antibiotic-sensitive organisms, but also in infections due to organisms resistant to one or more of the following antibacterial agents: penicillin, ampicillin, carbenicillin, tetracyclines, erythromycin, chloramphenicol, cephalosporins, kanamycin, gentamicin, tobramycin, and sulphamethoxazole-trimethoprim.

Many Gram-negative pathogens are resistant to penicillins and cephalosporins through the action of the β-lactamases which are produced by these pathogens. 'Mefoxin' is remarkably stable in the presence of these bacterial β-lactamases, both penicillinases and cephalosporinases. Hence, the clinical efficacy of 'Mefoxin' extends to many infections caused by such pathogens.

'Mefoxin' is indicated for the treatment of the following infections caused by sensitive bacteria:
Peritonitis and other intra-abdominal and intrapelvic infections; female genital tract infections; septicaemia; urinary tract infections; respiratory tract infections; bone and joint infections; and skin and soft-tissue infections.

'Mefoxin' is indicated for adjunctive therapy in the surgical treatment of infections, including abscesses, infection complicating hollow visceral perforations, cutaneous infections, and infections of serous surfaces, whether caused by aerobes, mixed aerobes and anaerobes, or anaerobes.

Microbiology
'Mefoxin' is active *in vitro* against:
Aerobic bacteria
Gram-positive cocci including: *Staphylococci*, (including coagulase-positive, coagulase-negative, and penicillinase-producing strains); Group A beta-haemolytic streptococci *(Streptococcus pyogenes)*; Group B beta-haemolytic streptococci *(Streptococcus agalactiae)*, *Streptococcus pneumoniae (Diplococcus pneumoniae)*; other streptococci (except group D streptococci including enterococci, most strains of which are resistant, e.g. *Streptococcus faecalis*). *Gram-negative cocci* including: *Neisseria gonorrhoeae* (including penicillinase-producing strains); *Neisseria meningitidis*. *Gram-negative rods (facultative anaerobes)* including *Escherichia coli*, *Klebsiella pneumoniae*, Klebsiella spp., *Proteus mirabilis*, *Proteus* (indole-positive) *Proteus vulgaris; Proteus rettgeri, Proteus morganii, Haemophilus influenzae, Serratia marcescens;* Providencia spp., Salmonella and Shigella spp.

Anaerobic bacteria
Gram-positive cocci including: Peptococcus spp.; Peptostreptococcus spp., Micro-aerophilic streptococcus. *Gram-positive rods including:* *Clostridium perfringens;* Clostridium spp.; Eubacterium spp., *Propionibacterium acnes*. *Gram-negative cocci including:* Veillonella spp. *Gram-negative rods including: Bacteroides fragilis, Bacteroides melaninogenicus*, Bacteroides spp. (including both penicillin-susceptible and penicillin-resistant strains); Fusobacterium spp.

'Mefoxin' is active against some strains of the following bacteria: *Acinetobacter calcoaceticus var. anitratum (Herellea vaginicola); Acinetobacter calcoaceticus var. lwoffi (Mima polymorpha); Alcaligenes faecalis*, Citrobacter spp. and Flavo-bacterium spp.; Enterobacter spp.

'Mefoxin' is not active against Pseudomonas, most strains of enterococci and many strains of *Enterobacter cloacae*.

Dosage and administration
'Mefoxin' may be administered intravenously or intramuscularly. (See reconstitution directions for each route below.) Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organisms, and condition of the patient.

Therapy may be started while awaiting the results of susceptibility testing.

Dosage: The usual adult dosage is 1 g or 2 g of 'Mefoxin' every eight hours. (See chart.)

In adults with renal insufficiency an initial loading dose of 1 g or 2 g may be given. After a loading dose, the following recommendations for *maintenance dosage* may be used as a guide.

Usual adult dosage

Type of infection	Dose	Frequency	Total daily dosage
Uncomplicated	1 g	Every 8 hours (occasionally every 6 hours)	3 g (4 g)
Moderately severe or severe	2 g	Every 8 hours (occasionally every 6 hours)	6 g (8 g)
Infections generally needing antibiotics in higher dosage	3 g (2 g)	Every 6 hours (Every 4 hours)	12 g

Maintenance dosage of 'Mefoxin' in adults with reduced renal function

Renal function	Creatinine clearance (ml/min)	Dose	Frequency
Mild impairment	50-30	1-2 g	Every 8-12 hours
Moderate impairment	29-10	1-2 g	Every 12-24 hours
Severe impairment	9-5	0.5-1 g	Every 12-24 hours
Essentially no function	<5	0.5-1 g	Every 24-48 hours

In the patients undergoing haemodialysis, the loading dose of 1 to 2 g should be given after each haemodialysis, and the maintenance dose should be given as indicated in the table above.

Intravenous administration: reconstitute 'Mefoxin' with Water for Injection BP. 1 g is soluble in 2 ml. Although 'Mefoxin' is very soluble, for intravenous use it is preferable to add 10 ml of Water for Injection BP to the 1 g vial or the 2 g vial. Shake to dissolve and then withdraw entire contents of vial into syringe.

For direct intravenous injection, 'Mefoxin' may be slowly injected into

Outstanding clinical benefits

Wide-ranging activity against Gram-negative and Gram-positive pathogens, anaerobes as well as aerobes.

Unusually high resistance to β-lactamase degradation.

Highly active against *Bacteroides fragilis* and strains of *E coli,* Serratia, Klebsiella spp. and Proteus spp. (including indole positive strains) resistant to other antibacterial agents.

Offers high levels of active antibiotic in the body.

A record of relative safety comparable to the penicillins.

Prime indications include:

- Peritonitis, and other intra-abdominal and intrapelvic infections.
- Female genital tract infections
- Septicaemia
- Skin and soft tissue infections
- Bone and joint infections
- Urinary tract infections
- Respiratory tract infections (e.g. inhalation pneumonia)

Specific clinical profile

Mefoxin is exceptionally valuable wherever Gram-negative pathogens and anaerobes are involved in mixed infections. When mixed infections are suspected, therapy may be started while awaiting the results of susceptibility testing.

Mefoxin®

Cefoxitin sodium, MSD INJECTION

First of the cephamycins

he vein over a period of 3 to 5 minutes or may be given through the ubing when the patient is receiving parenteral solutions.

An intermittent intravenous infusion of 'Mefoxin' may be employed when large amounts of fluid are to be given. However, during nfusion of the solution containing 'Mefoxin', it may be advisable emporarily to discontinue administration of any other infusion solution at the same site (by using an appropriate IV infusion set).

A solution of 'Mefoxin' may also be given by continuous intravenous nfusion (see below for compatibility and stability).

ntramuscular administration ONLY
Reconstitute 'Mefoxin' 1 g with 2 ml of Water for Injection BP, or 0.5% or 1% lignocaine hydrochloride (without adrenaline) solution. Mefoxin' is given by deep injection into a large muscle mass. Avoid injection into a blood vessel.

Compatibility and stability
A solution of 'Mefoxin' in Water for Injection BP may be added to the ollowing solutions: 0.9% Sodium Chloride Injection BP, 5% or 10% Dextrose Injection BP, Dextrose and Sodium Chloride Injection 5%/0.9%, 5%/0.45%, or 4.3%/0.18%) Lactated Ringer's Injection USP, 5% Dextrose in Lactated Ringer's Injection, 5% or 10% invert sugar in water, 10% invert sugar in saline solution, 4.2% Sodium Bicarbonate Injection BP, M/6 Sodium Lactate Injection BP.

Mefoxin', as constituted to 1 g/10 ml with Water for Injection BP, Water for Injection BP preserved with parabens or benzyl alcohol, 0.9% Sodium Chloride Injection BP, or 5% Dextrose Injection BP, maintains satisfactory potency for 24 hours at room temperature, for 96 hours under refrigeration, and for 13 weeks in the frozen state.

'Mefoxin' can be administered concomitantly with such antibiotics as gentamicin, tobramycin, carbenicillin or amikacin. When 'Mefoxin' is administered with another antibiotic, they should not be mixed in the same syringe.

Contra-indications
Mefoxin' is contra-indicated in persons who have shown hypersensitivity to cefoxitin. In the absence of clinical experience, Mefoxin' should not be administered to patients who have shown hypersensitivity to cephalosporins.

Precautions
There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and other β-lactam antibiotics, penicillins, and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most β-lactam antibiotics.

Before therapy with 'Mefoxin', careful inquiry should be made concerning previous hypersensitivity reactions to β-lactam antibiotics. 'Mefoxin' should be given cautiously to penicillin-allergic patients.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. If an allergic reaction to 'Mefoxin' occurs, the drug should be discontinued.

The total daily dosage should be reduced when 'Mefoxin' is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see 'Dosage and administration') because high and prolonged serum antibiotic concentrations can occur from usual doses.

Interference with laboratory tests
A false-positive reaction to glucose in the urine may occur with reducing substances but not with the use of specific glucose oxidase methods.

Use in pregnancy
Use of the drug in women of childbearing potential requires that the anticipated benefits be weighed against possible hazards. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the foetus due to 'Mefoxin'. There are no controlled studies with 'Mefoxin' in pregnant women.

Nursing mothers
'Mefoxin' is excreted in human milk.

Infants and children
Pending the outcome of clinical trials in progress, the conditions for use of 'Mefoxin' in infants and children remain to be defined.

Side effects
'Mefoxin' is generally well tolerated. Side effects rarely require stopping treatment and usually have been mild and transient.

Local reactions
Thrombophlebitis has occurred with intravenous administration. Pain induration and tenderness after intramuscular injections have been reported.

Allergic
Maculopapular rash, urticaria, pruritus, eosinophilia, fever and other allergic reactions have been noted rarely.

Gastro-intestinal
Diarrhoea has been reported rarely.

Blood
Transient leucopenia and neutropenia have been reported. Some individuals, particularly those with azotaemia, may develop positive direct Coombs tests during therapy with 'Mefoxin'.

Liver function
Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase have been reported rarely.

Kidney
Elevations in serum creatinine and/or blood urea levels have been observed. The role of 'Mefoxin' in changes in renal function test is difficult to assess, since factors predisposing to pre-renal azotaemia or to impaired renal function usually have been present.

Presentation
In vials containing 1 g or 2 g of cefoxitin as the sodium salt. Each gram of cefoxitin contains approximately 51.5 mg (2.2 mEq) sodium.

Product licence numbers: 1 g, 0025/0130; 2 g, 0025/0131

Product authorisation numbers: 1 g, PA 35/42/1; 2 g, PA 35/42/2

Issued October 1978

Additional information is available to the medical profession on request.

Basic NHS cost is £4.47 for the 1 g vial, and £8.94 for the 2 g vial.

MSD
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Merck Sharp & Dohme Limited,
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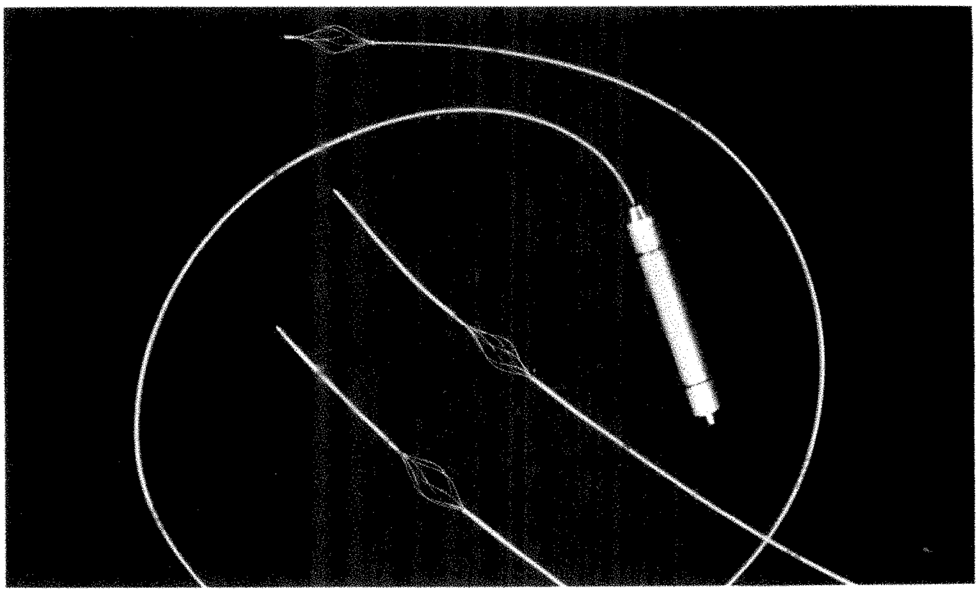
fister-Schwartz Stone Retriever

New, low cost six wire helical pear-shaped basket for removal of ureteral calculi



- ✱ central cable cannot kink, in normal use
- ✱ catheter less than 3.7 French permits easier introduction past ureteral stone
- ✱ basket can be rotated in either direction – important when trying to engage a difficult calculus
- ✱ long integral filiform tip cannot become detached during procedure, yet is pliable
- ✱ two sizes available with plain tip or 6cm filiform tip. Small basket opens to 8.0mm length x 2.4cm, large basket to 11.0mm length x 2.8cm.
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An Ultrastructural Study on the Effects of Warm Ischaemia on the Inosine-protected Kidney

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Department of Urology, St Bartholomew's Hospital; Department of Pathology, St Paul's Hospital; Institute of Urology, London

Summary—Unperfused, saline-perfused and inosine-perfused rat kidneys were subjected to various times of warm ischaemia with and without resumption of blood flow. Tissues were examined with a transmission electron microscope.

Inosine has a protective effect on the epithelial cells of the proximal convoluted tubules, where microvilli are less damaged by ischaemia than those of the proximal convoluted tubular cells of the control animals. There is also a much higher ratio of autophagic vacuoles to lysosomes present in cells of inosine-treated kidneys, reflecting their ability to sequester and digest organelles damaged during ischaemia and thus protect themselves from degradation products.

A major effect of inosine seems to be the preservation of the organelles and brush border of the cells of the proximal tubule during warm ischaemia.

The purine nucleoside inosine has been shown to protect the kidney during warm ischaemia as regards renal function and tissue nucleotide resynthesis (Fernando *et al.*, 1976, 1977). The urinary excretion of gamma glutamyl transpeptidase (γ-GT), an enzyme located in the proximal tubular brush border, was lower after warm ischaemia if the kidney was protected with inosine (unpublished observation). This indicated that inosine might prevent damage to the brush border of the proximal tubule cell which is important in the maintenance of renal function.

This study was undertaken to investigate the morphological features of renal injury during warm ischaemia with and without blood reflow and the effects of perfusion with physiological saline solution or inosine in saline.

Materials and Methods

Thirty-two specified-pathogen-free (SPF) male Wistar rats, 250-350 g body weight (bw) were used in this study. Anaesthesia was by intraperitoneal pentobarbitol (45 mg/kg bw initially with supplementary doses as indicated). Animals that were heparinised had 400 i.u. sodium heparin/kg bw intravenously.

The control and experimental groups were as shown in Table 1. Methods of perfusion and induction of ischaemia were as previously described (Fernando *et al.*, 1976); the inosine solution (4% inosine in 0.9% saline) was prepared by previously reported methods (Fernando *et al.*, 1977). Contralateral nephrectomy was performed 15 min before the end of the period of ischaemia.

Table 1 Control and Experimental Groups

Normal control	(2)			
Warm ischaemia without blood reflow (systemic heparin, contralateral nephrectomy)				
	Period of warm ischaemia (min)			
No perfusion	30 (1)	60 (1)	120 (1)	
0.9% NaCl perfusion	30 (1)	60 (1)	120 (1)	
4% inosine in saline perfusion	30 (2)	60 (2)	120 (2)	
No heparin, no perfusion	30 (1)	60 (1)	-	
Standard 60 min warm ischaemia and blood reflow (systemic heparin, contralateral nephrectomy)				
	Reflow period			
	Min.	*Min.*	*Days*	*Days*
No perfusion	30 (1)	60 (1)	3 (1)	7 (1)
0.9% NaCl perfusion	30 (1)	60 (1)	3 (1)	7 (1)
4% inosine in saline perfusion	30 (2)	60 (2)	3 (2)	7 (2)

Number of rats in parentheses.

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Table 2 Ultrastructural Findings After Warm Ischaemia Without Blood Reflow

Perfusion	*Warm ischaemia time (min)*	*Proximal convoluted tubule*			*Endothelium*	
		Nucleus	*Mitochondria*	*Microvilli*	*Arteriolar*	*Capillary*
None	30	+	+	+	n	n
None	60	+ +	+ + +	+ +	n	n
None	120	+ + +	+ +	+ + +		n
0.9% NaCl	30	+ +	+ + +	+		+
0.9% NaCl	60	+ +	+ + +	+ +	n	+
0.9% NaCl	120	+ + +	+ + +	+ + +	n	+ +
4% inosine in saline	30	+	n	+ +	+ + +	n
4% inosine in saline	60	+	n	+	+ + +	n
4% inosine in saline	120	+ +	+	+	+ + + +	+
No heparin, no perfusion	30	+ + +	+ +	+ + +		n
No heparin, no perfusion	60	+ + +	+ +	+ + +		

n = normal.
+ to + + + + = damage.

For electron microscopy, slices from the kidneys were rapidly diced and immersed for one hour in osmium tetroxide for fixation (Palade, 1952). After fixation, tissues were dehydrated in ascending concentrations of acetone, infiltrated with and then embedded in TAAB resin (TAAB Laboratories, Reading); 1 μ thick sections were cut on an LKB Ultrotome III, stained with toluidine blue and examined with the light microscope; thin sections were cut with a diamond knife and stained with saturated alcoholic uranyl acetate and lead citrate (Reynolds, 1963) and viewed with an AEI 6M electron microscope.

Results

Normal Controls (Fig. 1)

Cells of the proximal convoluted tubules (PCT) had round or oval nuclei containing dispersed chromatin and numerous long, slender mitochondria arrayed in a regular manner perpendicular to the basement membrane. The microvilli of the brush border were regular with sharply outlined membranes. The lumen was generally closed.

Experimental Animals (Figs. 2-8)

The cells of the PCT showed increasing damage as the time of ischaemia was prolonged. The chromatin of the nuclei became marginated (1^+) or coarsely clumped (2^+) and the nucleus crenellated (3^+). The mitochondria were disorganised with respect to the basement membrane (1^+), or swollen (2^+) with loss of cristae (3^+) and loss of limiting membrane (4^+). The microvilli became

Table 3 Ultrastructural Findings After 60 Minutes' Warm Ischaemia With Blood Reflow

Perfusion	*Blood reflow time*	*Proximal convoluted tubule*			*Endothelium*	
		Nucleus	*Mitochondria*	*Microvilli*	*Arteriolar*	*Capillary*
None	30 min	+ + +	+ + + +	+ + + +	n	
None	60 min	+	+ +	+ +	+ +	n
None	3 days	n	+	+	n	n
None	7 days	n	+	+	n	n
0.9% NaCl	30 min	+ + +	+ + +	+ + + +		+
0.9% NaCl	60 min	+	+ +	+ +	+ +	+
0.9% NaCl	3 days	n	n	+	n	+
0.9% NaCl	7 days	n	n	n	n	+
4% inosine in saline	30 min	+ +	n	+	+ + + +	n
4% inosine in saline	60 min	n	+	n	+ +	+
4% inosine in saline	3 days	n	n	n	+ +	n
4% inosine in saline	7 days	n	n	n	+ +	n

n = normal.
+ to + + + + = damage.

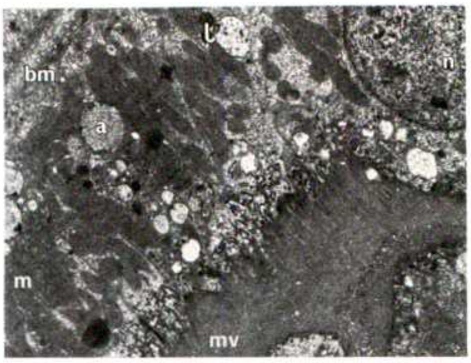

Fig. 1 Normal proximal convoluted tubule (PCT), n—nucleus, mv—microvilli, m—mitochondria, l-lysosome, bm—basement membrane, a—autophagic vacuole. (× 7500.)

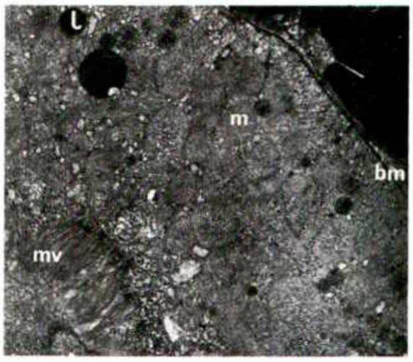

Fig. 2 PCT of unperfused kidney after 60 min of warm ischaemia. (× 12,000.)

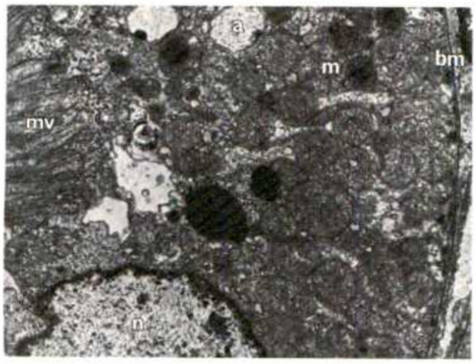

Fig. 3 PCT of saline-perfused kidney after 60 min of warm ischaemia. (× 12,000.)

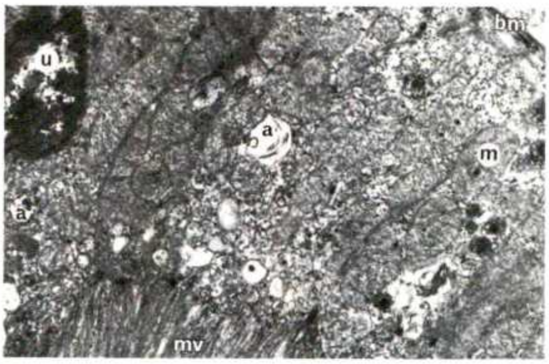

Fig. 4 PCT of inosine-perfused kidney after 60 min of warm ischaemia. (× 12,000.)

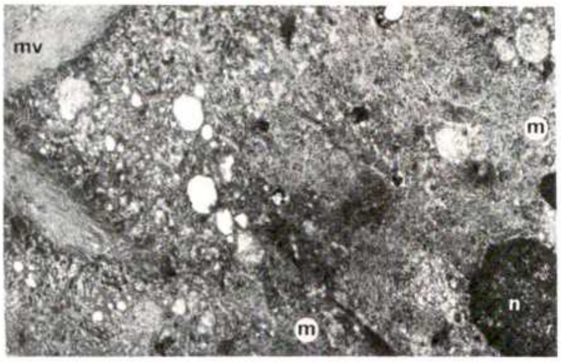

Fig. 5 PCT of unperfused kidney after 60 min of warm ischaemia and 60 min of blood reflow. (× 12,000.)

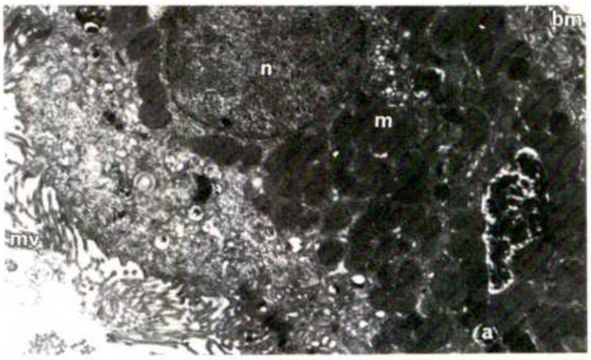

Fig. 6 PCT of saline-perfused kidney after 60 min of warm ischaemia and 60 min of blood reflow. (× 12,000.)

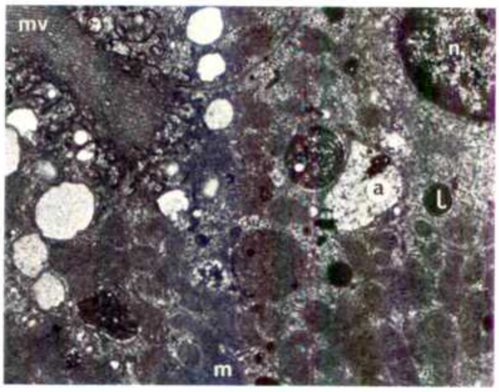

Fig. 7 PCT of inosine-perfused kidney after 60 min of warm ischaemia and 60 min of blood reflow. (× 12,000.)

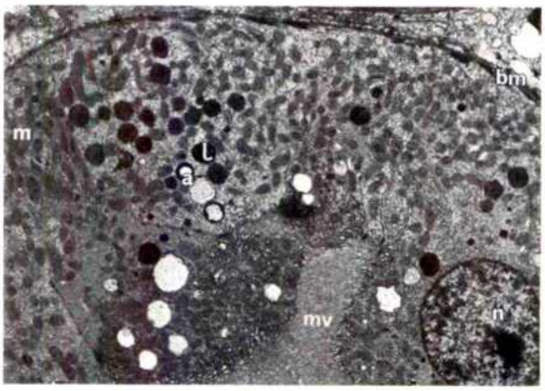

Fig. 8 PCT of inosine-perfused kidney after 60 min of warm ischaemia and 7 days of blood reflow. (× 5000.)

"fuzzy" (1^+), disorganised (2^+) or indistinct, with debris in the lumen (3^+); rarely the microvilli were absent (4^+).

The endothelial cells lining the intertubular capillaries and arterioles showed intracellular swelling (1^+). At times these cells were vacuolated or ruptured $(2\text{-}4^+)$. These observations are summarised in Tables 2 and 3.

There were also changes in the numbers of lysosomes and autophagic vacuoles within the PCT cells. These findings are shown on the graphs in Figures 9, 10, 11 and 12.

Discussion

In the 2 untreated animals tissue from kidneys was viewed under the electron microscope to control fixation artifacts. These tissues met the criteria for good fixation as suggested by Latta *et al.* (1967).

Comparison of tissues from unperfused and saline-perfused kidneys shows that there is an increasing amount of damage with increasing time of warm ischaemia. The observations of Glaumann *et al.* (1975) on ischaemic damage to the PCT cells of the unperfused kidney were similar. How-

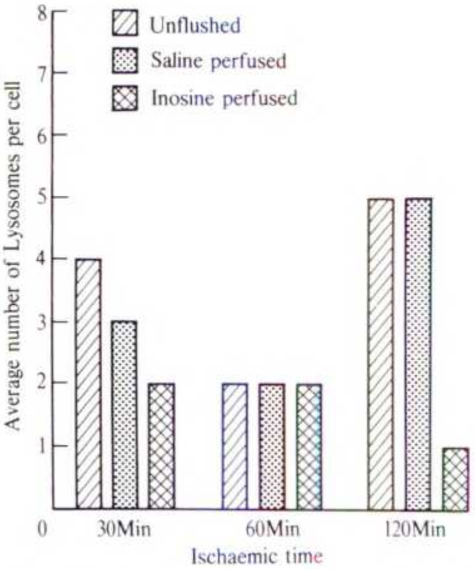

Fig. 9 Average number of lysosomes per PCT cell with increasing ischaemic time.

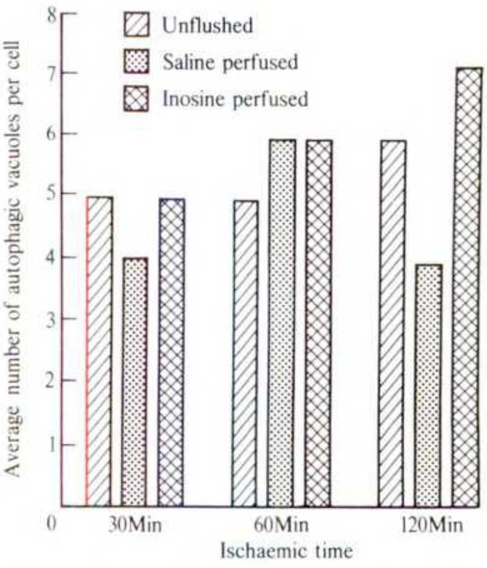

Fig. 10 Average number of autophagic vacuoles per PCT cell with increasing ischaemic time.

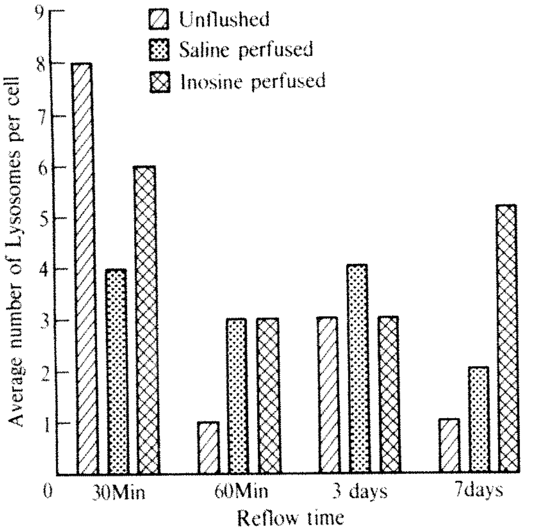

Fig. 11 Average number of lysosomes per PCT cell after 60 min of ischaemia and varying times of reflow.

ever, in the inosine-perfused kidney there was less damage to the cells of the PCT during periods of ischaemia; this was most marked in the mitochondria, which remained normal during the shorter intervals and showed only marginal damage after 120 min. Similarly there was increased damage to the microvilli of the PCT cells in unperfused and saline kidneys with increase in duration of ischaemia, while in the inosine-perfused kidney the microvilli, damaged at 30 min, improved to show only some fuzziness after the longer intervals of ischaemia.

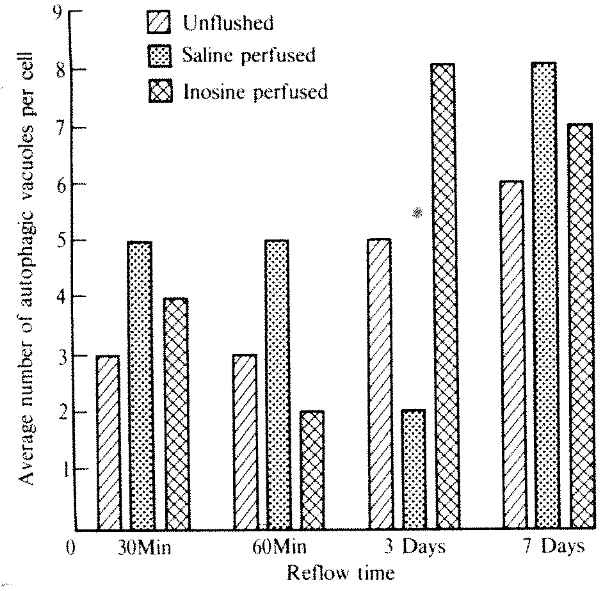

Fig. 12 Average number of autophagic vacuoles per PCT cell after 60 min of ischaemia and varying times of reflow.

When examining lysosomes and autophagic vacuoles, differences were seen under the various experimental conditions in the numbers of these organelles present in the PCT cells. The average number of primary lysosomes per cell was reduced in the inosine-perfused PCT cells as the number of autophagic vacuoles increased, and this difference was most marked after 120 min of ischaemia. The significance of the formation of autophagic vacuoles and their protective role during ischaemia has been elucidated by Ericsson (1969) who postulated that the formation of autophagic vacuoles from lysosomes is the end result of a sequestering process by which damaged organelles are engulfed by lysosomes and many of their components digested by lytic enzymes present in the lysosomes. The usable chemical components are re-utilised by the cell, the autophagic vacuole representing the "indigestible" remnant. Thus the cell is protected from the effects of focal damage occurring during a period of ischaemia. This process of walling-off and digestion is an energy-requiring process and it is here that the purine nucleoside, inosine, may be important. It was previously found that inosine-perfused kidneys maintained higher tissue AMP, ADP and IMP concentrations during warm ischaemia, and post-ischaemic ATP resynthesis was rapid (Fernando *et al.*, 1976). Morphologically the protective effect of inosine was evident at 120 min of ischaemia, when the high number of autophagic vacuoles, along with a marked drop in the number of lysosomes, indicated that the energy-requiring walling-off process was protecting the cell against irreversible damage. The numbers of autophagic vacuoles and lysosomes in the PCT cells of unperfused and saline-perfused kidneys did not show these marked changes. Thus it is interesting to compare the changes in these organelles after various times of blood reflow after a standard period of 1 hour's warm ischaemia. The mitochondria were more damaged in the PCT cells of the saline-perfused kidney than the inosine-perfused one after the shorter periods of reflow, though in both groups the mitochondria were normal on day 3, while they were still swollen on day 7 in the tissues of the unperfused animal. Brush border recovery was also more rapid in the inosine-perfused kidneys. After 30 min of reflow the microvilli showed an organised pattern, though the crispness of the limiting membranes was not present. After 60 min of blood reflow the microvilli were "crisp" and organised and remained so after 3 and 7 days' reflow.

In the saline-perfused kidney the microvilli returned to normal after 7 days' reflow, while tissues from unperfused kidneys never recovered completely during the period studied.

When examining the lysosome:autophagic vacuole ratios, it is again evident that inosine plays a role in cell protection.

Increase in the number of autophagic vacuoles seen on day 3 in the inosine-perfused kidneys was not seen until day 7 in the saline-perfused ones. Here too the unperfused kidney is at a marked disadvantage.

The non-heparinised animals subjected to 30 and 60 min of warm ischaemia were compared to heparinised ones similarly treated. The effects of ischaemia were somewhat more rapid in the non-heparinised animals, especially as regards the brush border.

The endothelial cells of the intertubular capillaries were normal in all inosine-perfused kidneys, in contrast with the saline-perfused ones where some cellular swelling was seen under all experimental conditions. Unperfused kidneys also had normal endothelial cells lining the capillaries.

However, the arterioles in the inosine-perfused kidneys showed swollen endothelial cells under conditions of warm ischaemia and subsequent blood reflow. This did not abate entirely even after 7 days, whereas endothelial cells from arterioles of unperfused and saline-perfused kidneys were normal after 3 days of blood reflow. This is a puzzling finding in view of the minimal depression of function if the kidneys were perfused with inosine before 60 min of warm ischaemia (Fernando *et al.*, 1976).

The present series of experiments was done to examine the effects of inosine on the ultrastructural morphology of the ischaemic kidney. The results of this study indicate that one of the chief effects of inosine may be the provision of the energy required for the orderly maintenance of the microvilli of the cells of the proximal convoluted tubules and for the repair of localised damage sustained by these cells during warm ischaemia.

Acknowledgements

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Ectopic Kidneys With and Without Fusion

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Summary—Sixty-one patients with renal ectopia have been reviewed. Most presented with a palpable mass, abdominal pain or microscopic haematuria. Thirteen patients were treated surgically, usually by nephrectomy; 17 required no treatment and 31 were treated symptomatically.

Renal ectopia with and without fusion is relatively rare (McDonald and McLellan, 1957). It causes atypical and vague symptoms and may present as a mass in the lower abdomen. In women, it may interfere with pregnancy.

Patients

Sixty-one cases of renal ectopia with and without fusion were diagnosed in the 15-year period 1961 to 1975 (Table 1). The age at presentation ranged from 8 to 75, with the majority presenting between the ages of 30 and 60 years. There was no significant difference between the incidence in males and females except in the cases of pelvic ectopia, where there were 15 females and 7 males.

The left kidney was more often found in the ectopic position: in simple unilateral ectopia the ratio of left to right was 2:1; in crossed renal ectopia without fusion it was 5:0, and in unilateral fused kidneys it was 3:2. The clinical features leading to the diagnosis are summarised in Table 2. The diagnosis was confirmed in all cases by excretion urography and nephrotomography. Cystoscopy and retrograde pyelography were carried out in 19 cases, renal angiography in 6 and renal scanning in 5.

A coexistent congenital abnormality was found in 10 cases. In 7 there was another abnormality of the genitourinary tract: 2 hydronephroses, 1 hydroureteronephrosis, 1 renal malrotation, 2 renal ageneses and 1 hypospadias; there was 1 case of utero-vaginal hypoplasia and 2 children had spina bifida.

The management is summarised in Table 3. Seventeen patients (of whom 13 had been diagnosed incidentally on X-ray) required no treatment. Thirty-one patients who presented with pain or symptoms related to infection, stone or hydronephrosis were treated symptomatically.

Thirteen patients (21%) were treated by surgery. In 10 cases the ectopic kidney was removed—for hydronephrosis in 7, for renal tumour in 2, and

Table 1 Classification of 61 Cases of Renal Ectopia

		Number of cases
(1) Simple renal ectopia		
Unilateral:	thoracic dystopia	1
	abdominal ectopia	6
	iliac ectopia	19
	pelvic ectopia	20
	solitary pelvic kidney	2
Bilateral		1
(2) Crossed renal ectopia without fusion		
Unilateral		5
Bilateral		—
(3) Fused kidneys		
Unilateral:	sigmoid kidney	2
	L-shaped kidney	2
	elongated kidney	1
Bilateral	concrescent kidney	2
Total		61

Table 2 Presentation in 61 Cases of Renal Ectopia

Presentation	*Number*	*(%)*
Colic in ectopic kidney	12	19
Abdominal pain	17	27
Palpable mass	19	31
Gross haematuria	11	18
Microscopic haematuria	15	24
Bladder symptoms	14	22
Gastrointestinal symptoms	10	16
Pelvic symptoms in women	8	13
Hypertension	2	3
Renal failure	2	3

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Table 3 Treatment in 61 Cases of Renal Ectopia

Abnormality	*Number of cases*	*No treatment*	*Conservative (symptomatic) treatment*	***Surgical treatment***	
				Nephrectomy	***Conservative***
Thoracic dystopia	1		1		
Abdominal ectopia	6	3	2	1	
Iliac ectopia	19	5	8	6	
Pelvic ectopia	22	6	11	3	2
Bilateral simple ectopia	1		1		
Crossed renal ectopia without fusion	5	2	3		
Unilateral crossed ectopia with fusion	5	1	3		1
Bilateral fused kidney (concrescent kidney)	2		2		
Total	61	17	31	10	3

for persistent pain in 1. Two patients were treated by pyelotomy, 1 for stone and the other for a papillary tumour of the renal pelvis in a solitary kidney. A left uretero-lithotomy was performed in 1 patient with a unilateral fused kidney. An extraperitoneal surgical approach was made in all cases. The post-operative course was uneventful, except for the patient with papilloma in the pelvis of a solitary kidney, who died from a myocardial infarct on the first post-operative day.

Discussion

An abnormality of the ureteric bud may cause fusion or ectopia. Wilmer (1938) considered that the umbilical arteries could obstruct the ascent of the metanephros and result in early fusion. Others considered that the vascular supply of the kidneys could become established if there was obstructed ascent of the embryonic kidneys, thus keeping the kidney in the ectopic position (Borell and Fernström, 1954; Pathak, 1965).

Thoracic renal ectopia has been attributed to delay in the transformation of the mesonephros to metanephros (Malter and Stanley, 1972), which results in the continuation of the ascent beyond the eighth embryonic week (at which time the diaphragm has not completely closed).

The clinical symptoms and findings related to renal ectopia do not have special characteristics and in 28% of the present series the diagnosis was made either incidentally on X-ray or, more rarely, at operation. In 44% a coexistent secondary lesion led to the diagnosis of the underlying abnormality.

In general, the finding of a lower abdominal or retroperitoneal mass, together with vague abdominal symptoms, must raise the suspicion of an ectopic kidney. The diagnosis may be confirmed by excretion urography with nephrotomography, but more detailed investigations may be required to determine the exact anatomy of the renal abnormality. To know the exact vascular formation prior to a surgical procedure is valuable.

When the congenital abnormalities are asymptomatic and without complications, treatment is not required. Surgical treatment is generally indicated for complications such as stone or obstruction.

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Effects of Therapy with Bendroflumethiazide in Patients with Recurrent Renal Calcium Stones

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Summary—Forty-four patients with recurrent formation of calcium-containing renal stones were treated with bendroflumethiazide for at least 2 years. Prior to treatment each patient had formed, on average, one stone per year for 8 years; during treatment only 4 patients formed new stones.

A reduction in urinary calcium excretion was seen in almost all patients irrespective of their initial urinary calcium level. The apparent clinical benefit was not related to pre-treatment urinary electrolyte levels.

Side effects were slight: one patient developed symptomatic hyperuricaemia and in one case sustained hypercalcaemia was found. Long-term treatment with thiazides appears to be a safe and effective method for the prevention of recurrent calcium stones.

The formation of calcium-containing renal stones is a large and apparently increasing problem. Recent population studies indicate that over 10% of adult males will experience stones at least once (Ljunghall, 1977) and the recurrence rate is close to 50% within 10 years (Williams, 1963; Ljunghall, 1977). Multiple and frequent recurrences occur in a large number of cases, causing both individual discomfort and a considerable impact on the health services.

In most renal stone formers no single disorder is found to be responsible (Nordin, 1973). Stone formation and growth are usually regarded as the final result of an accumulation of unfavourable events (risk factors) in association with a relative lack of protecting, favourable factors (Robertson *et al.*, 1978). Among the many risk factors postulated for calcium stone formation a high urinary calcium level is of great importance. Epidemiological studies have shown that the risk of stone formation increases in proportion to the urinary calcium output over the whole range of values and that there is no lower limit below which no renal stones are formed (Ljunghall and Waern, 1977).

A logical approach to the prevention of stone formation should therefore be an attempt to reduce urinary calcium. It has long been recognised that thiazides reduce the excretion of calcium (Lamberg and Kuhlbäck, 1959) and since their use in other disorders has been seen to be comparatively safe and free from side effects, it was suggested that they might be safely used to prevent the formation of recurrent calcium stones (Yendt *et al.*, 1966). In subsequent studies, where larger numbers of patients have been observed, beneficial effects have also been reported (Yendt and Cohanim, 1973; Coe, 1977).

The present study has been undertaken to evaluate the long-term clinical and metabolic effects of the use of thiazides in patients with recurrent calcium stone formation. Therapy has been instituted regardless of the initial levels of urinary calcium in order to see if favourable effects would also occur with a reduction of urinary calcium within the normal range.

Patients and Methods

All patients referred to our stone clinic for evaluation of recurrent stone formation undergo a detailed out-patient investigation. This includes repeated determination of serum and urinary electrolytes, measurement of serum and urinary uric acid, urinary oxalate and a qualitative test for cystine (nitroprusside reaction). Urine cultures, urine analysis, X-ray of the urinary tract and stone analysis are performed. All patients also undergo a short-term ammonium chloride loading test (Backman *et al.*, 1976a). The urinary excretion of β_2-microglobulin is determined as an index of tubular proteinuria (Backman *et al.*, 1976b). Urinary cyclic AMP (cAMP) is determined by a radioimmunoassay method (Wålinder

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et al., 1978) and serum parathyroid hormone (PTH) analyses are performed by Medicinsk Laboratorium, Copenhagen.

This study presents the results of thiazide therapy in 44 consecutive patients (34 males, 10 females) with a mean age of 41 years (range 23 to 65 years). All patients had formed calcium-containing stones within the preceding year. All patients had repeatedly normal serum calcium values. One of them had slight hyperuricaemia (serum urate 470 μmol/l), 2 had a medullary sponge kidney, 5 had a defective renal tubular acidification capacity and 6 had tubular proteinuria (urinary β_2-microglobulin > 370 μg/24 h).

Assessment of Stone Activity

Old records, patient history and previous radiographic studies were used to estimate stones formed by each patient before treatment. New stones were defined by the passage, removal or radiographic visualisation of a stone that was not seen on previous radiographs. Multiple stones occurring in clusters were classified as a single stone incident.

Treatment and Follow-up

After informed consent was obtained, therapy with bendroflumethiazide (Salures-K^{R}) was instituted. The tablets contained 2.5 mg bendroflumethiazide and 0.57 g potassium chloride and were given twice daily. Biochemical investigations were performed after 1, 3 and 6 months and thereafter at regular 6-monthly intervals. The average length of follow-up is at present 30 months and all patients have been treated for at least 2 years.

Control Group

The natural history of stones was followed in a group of 27 patients with idiopathic formation of recurrent calcium-containing stones, all of whom had been investigated by means of the same outpatient protocol. These patients were not on prophylactic treatment, either because they preferred to wait and see or because, in some instances, their disease was not considered metabolically active enough to justify medical therapy. This group of patients, which thus was not randomly selected, was followed to provide some indication of the value of the general medical advice and follow-up which is given to all patients in our stone clinic.

Results

Effects on Calcium Metabolism

The effects of treatment with bendroflumethiazide on serum and urinary electrolytes are shown in the table. The urinary calcium output decreased by approximately 40% within the first month and remained at this lower level throughout the follow-up. All but 4 patients showed a reduction in urinary calcium excretion. This reduction was greatest among those with the highest initial levels but it was also evident in subjects with pretreatment values within the normal range (Fig. 1).

There was a small increase in serum calcium concentration during the first month, but in most patients this was less than 0.1 mmol/l. Nine patients had some values above the upper limit of normal (2.60 mmol/l) while on treatment, but

Table Biochemical Effects of Treatment with Bendroflumethiazide in 44 Recurrent Calcium Stone Formers (Mean values ± SD)

	Before treatment	*Months on treatment*		
		1	*12*	*24*
Serum electrolytes (mmol/l)				
Calcium	2.44 ± 0.10	2.48 ± 0.10	2.53 ± 0.10*	2.48 ± 0.09
Magnesium	0.80 ± 0.05	0.78 ± 0.07	0.75 ± 0.05	0.77 ± 0.07
Potassium	4.3 ± 0.3	3.9 ± 0.2†	3.8 ± 0.4†	3.9 ± 0.4†
Phosphate	0.97 ± 0.18	0.92 ± 0.20	0.92 ± 0.18	0.91 ± 0.20
Serum uric acid (μmol/l)	246 ± 64	295 ± 74†	337 ± 83†	327 ± 77†
Urinary electrolytes (mmol/24 h)				
Calcium	8.4 ± 2.7	5.9 ± 2.3†	5.7 ± 2.3†	5.8 ± 1.8†
Magnesium	4.3 ± 1.2	5.0 ± 1.8†	5.2 ± 2.3†	5.2 ± 1.0
Urinary Mg/Ca	0.60 ± 0.18	0.91 ± 0.30†	1.19 ± 1.12†	1.21 ± 1.70†
Urinary uric acid (mmol/24 h)	3.3 ± 1.1	3.1 ± 0.8	3.5 ± 1.0	3.6 ± 1.2

* $P<0.05$, † $P<0.001$ compared to pre-treatment values (paired t-test).

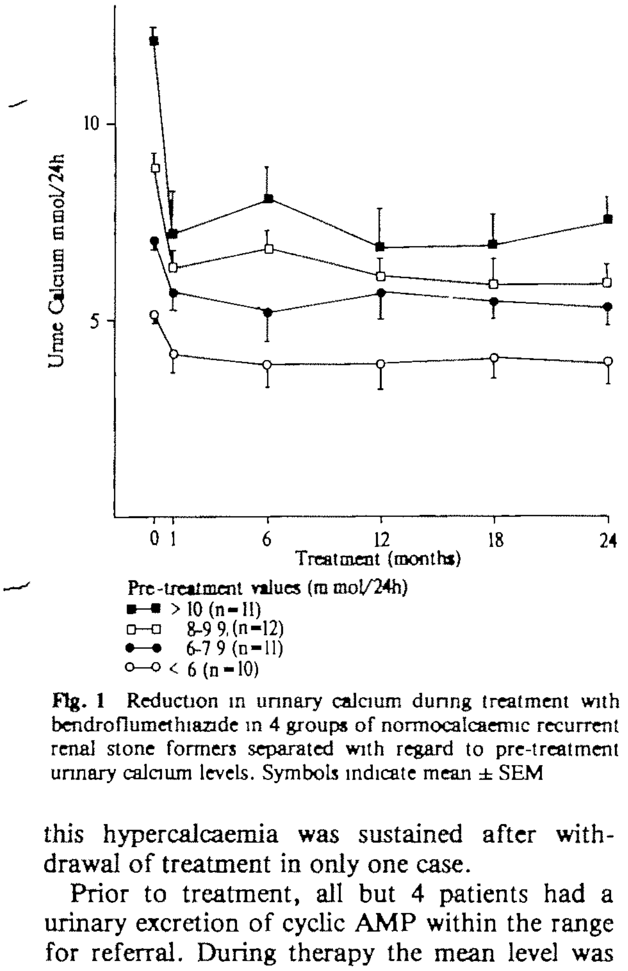

Fig. 1 Reduction in urinary calcium during treatment with bendroflumethiazide in 4 groups of normocalcaemic recurrent renal stone formers separated with regard to pre-treatment urinary calcium levels. Symbols indicate mean ± SEM

this hypercalcaemia was sustained after withdrawal of treatment in only one case.

Prior to treatment, all but 4 patients had a urinary excretion of cyclic AMP within the range for referral. During therapy the mean level was unchanged. The serum concentration of PTH was determined in all patients with hypercalcaemia; none showed a raised value.

Effects on Other Serum and Urinary Electrolytes

Excretion of urinary magnesium increased during the first month of treatment and remained at this higher level during follow-up, whereas the serum magnesium concentrations remained unchanged throughout the study (Table).

There was a sustained decrease in serum potassium concentrations within the first month of therapy. One patient developed asymptomatic hypokalaemia (serum potassium 2.9 mmol/l) after 6 months and required additional potassium supplements to regain normal serum concentrations.

Effects on Uric Acid Metabolism

The serum uric acid concentration increased within the first month and rose further during the first year of treatment. One patient, with a marginal pre-treatment hyperuricaemia, experienced symptoms suggestive of gout after 2 years' therapy, when his serum urate levels had increased to a maximum of 558 μmol/l. No other case of hyperuricaemia was recorded. Urinary uric acid excretion was not affected by the therapy; no patient

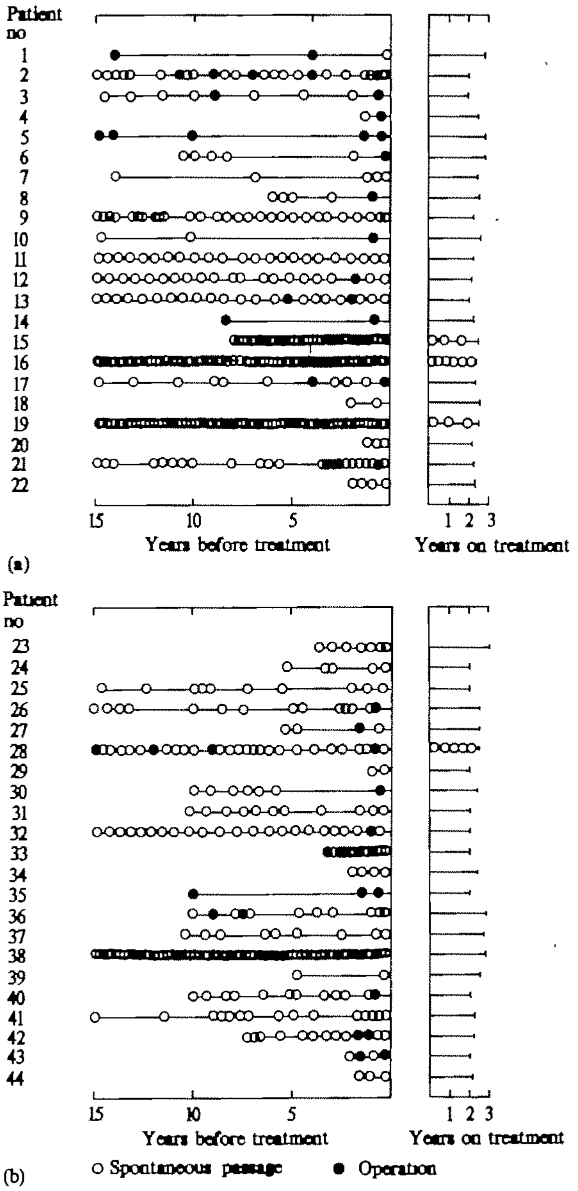

Fig. 2 Calcium stone formation before and during treatment with bendroflumethiazide. Each patient is shown as a horizontal line, and numbered according to age (oldest patient is No 1).

developed hyperuricosuria and no uric acid stones were formed during treatment.

Effects on Stone Formation

The individual pattern of stone formation for each patient before and during thiazide treatment is shown in Figure 2. Three patients had formed numerous stones each year before therapy. Although they continued to experience stones during treatment, 2 of them (Nos 16 and 19) showed a considerable reduction in stone formation. The remaining 41 patients had altogether formed about 400 stones during approximately 370 patient years from their first stones up to the start of thiazide treatment, i.e. one stone/year. During therapy (103 patient years) only one of them formed new stones. The only clear therapeutic failure (No. 28) did not show any effects of treatment on serum and urinary electrolytes and his serum uric acid levels were also unchanged.

Among the 29 patients in the control group 12 continued to form stones during an average observation period of 2 years (Fig. 3). Prior to the investigation their stone-forming frequency was estimated to be about 0.5 stones/year. During follow-up (65 patient years) the corresponding value was 0.4 stones/year.

Side Effects

Therapy was discontinued in one patient (No. 8) because of probable gout. Asymptomatic hypokalaemia, reversible upon additional potassium supplement, was recorded in one patient (No. 1). General discomfort (primarily dizziness, postural hypotension and fatigue) was experienced by 5 patients. These symptoms appeared to be partly dose-dependent and when treatment was gradually instituted over a period of weeks the patients tolerated the therapy.

Discussion

This study indicates that thiazide treatment is of clinical value in the prevention of calcium stone formation. The reports by Yendt and Cohanim (1973) and Coe (1977) are thus strongly supported.

The rationale for therapy with thiazides was suggested by the fact that thiazides reduce urinary calcium excretion and a high urinary calcium level is common amongst stone formers. In the present study, treatment was given not only to hypercalciuric patients but also to subjects with a calcium output within the normal range. This was based on the concept that any reduction in urinary calcium would be favourable as it would reduce the urinary activity product. Among our patients it appeared that therapy with thiazides was effective regardless of the initial urinary calcium values. In addition, patients with normal pretreatment urinary calcium reduced their output and experienced clinical benefit.

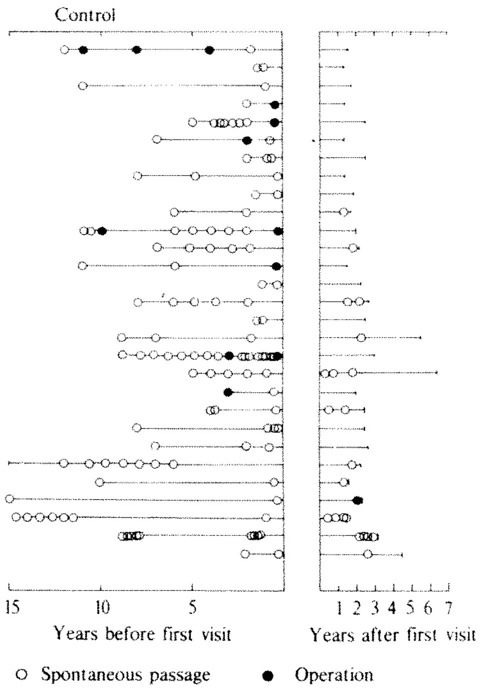

Fig. 3 Calcium stone formation before and after diagnostic evaluation in 29 patients without medical stone prophylactic treatment.

Although the effects on calcium excretion are likely to be of major importance, other biochemical effects of the treatment might also contribute to the preventive effect. Previous studies have reported an increased excretion of various inhibitors to crystallisation such as pyrophosphate (Pak, 1973), zinc (Cohanim and Yendt, 1975) and, as in the present study, magnesium (Yendt and Cohanim, 1973; Jörgensen and Brunner, 1974).

Magnesium inhibits the crystallisation of calcium oxalate *in vitro* and from epidemiological studies it appears that a low magnesium output, particularly when combined with a high urinary calcium level, is associated with an increased propensity to stone formation (Ljunghall and Waern, 1977). The raised magnesium output during long-term treatment might theoretically result in magnesium depletion with low intracellular magnesium concentrations. It is possible, therefore, that magnesium supplements should be given to patients on chronic thiazide therapy. In subjects with renal stones such supplementary treatment might increase the inhibitory effect on stone formation (Melnick *et al.*, 1971).

Only rarely does stone disease have a serious effect on a patient's everyday life and significant side effects are therefore unacceptable.

In the present study, as in earlier reports (Yendt and Cohanim, 1973; Coe, 1977), there were few problems with patient tolerance: one patient had a probable attack of gout and 5 experienced some general discomfort because of the drug's hypotensive effect.

The major possible biochemical side effect is a harmful influence on calcium metabolism, particularly on parathyroid function. Transient hypercalcaemia is a well known feature of thiazide treatment, although its cause is not fully known. Among possible contributory factors have been reported an increase in serum calcium-binding proteins (Yendt and Cohanim, 1973), sodium and volume depletion (Brickman *et al.*, 1972) and increased intestinal calcium absorption (Jörgensen and Transböl, 1974). Most of these effects, however, are evident only during short-term studies. Among patients on chronic thiazide treatment sustained hypercalcaemia is less common and, when present, it is in many cases apparently due to hyperparathyroidism (Christensson *et al.*, 1977).

The possibility of the drug having a stimulatory effect on parathyroid secretion has been suggested by animal experiments (Pickleman *et al.*, 1969) and by the finding of hyperparathyroidism in patients on thiazide therapy (Paloyan *et al.*, 1969). However, when measurements have been made of the serum levels of parathyroid hormone, usually no increase has been found (Stote *et al.*, 1972; Coe *et al.*, 1973). Furthermore, among 139 stone patients receiving thiazide treatment for up to 11 years, only 2 were found to have hyperparathyroidism (Yendt and Cohanim, 1973). A disproportionate increase in serum calcium in patients with disturbances of calcium metabolism has been reported during thiazide treatment, probably due to an inability to compensate for the renal retention of calcium provoked by the thiazides (Jörgensen, 1976). In some patients with marginal hypercalcaemia, therapy with thiazides might therefore contribute to an early diagnosis by revealing the underlying disorder (Adams *et al.*, 1970; Yendt and Cohanim, 1973). Among our patients, sustained hypercalcaemia was seen in one subject after cessation of treatment; he is free from clinical symptoms and is unwilling to undergo exploration of the neck, although he is suspected of having hyperparathyroidism.

Thiazides also affect the metabolism of uric acid. Raised serum urate levels are not uncommon (Healey *et al.*, 1959), although generally asymptomatic. Recently it has been suggested that uric acid disorders might also be involved in calcium stone formation (Coe and Kavalach, 1974), possibly by blocking of inhibitors (Robertson *et al.*, 1976). However, it is unlikely that thiazides will promote stone formation through this mechanism as the urinary uric acid excretion in the present study, as well as in previous reports (Yendt and Cohanim, 1973; Coe, 1977), is unchanged.

The progress of stone disease is characteristically variable and it is necessary to follow patients for a considerable time, preferably together with a control group, before valid conclusions can be drawn. In the present study, during a total of more than 100 patient years, only 4 patients formed new stones and only one experienced no reduction in stone recurrence, whereas among the controls stone formation continued after the initial diagnostic evaluation.

It would be valuable if the long-term clinical effects of therapy could be anticipated at an early stage during treatment, *e.g.* by the use of an *in vitro* test of the propensity to crystallisation. This would permit the identification of patients unlikely to respond to treatment and they could then be transferred to other treatment programmes. Few such studies have been performed on stone patients on thiazides. When the activity product has been calculated it has been shown to be reduced in all cases, primarily as the result of the reduction in urinary calcium (Pak, 1973). It has also recently been reported that thiazides, in addition to decreasing urine calcium excretion and increasing urine magnesium excretion, also decrease urinary brushite saturation, and thus possibly prevent spontaneous nucleation and crystal growth of calcium phosphate (Pylypchuk *et al.*, 1978). In the same study it was also suggested that thiazides possess the ability to prevent crystal growth on an organic matrix, as *in vitro* studies showed decreased collagen calcification.

The apparent clinical benefit of thiazide treatment in calcium stone formers is probably not restricted to the effects of electrolyte excretion and consequently, as in the present study, therapy with thiazide diuretics could also be expected to prevent stone recurrence in patients with apparently normal urinary electrolytes.

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Dietary Treatment of Idiopathic Hypercalciuria

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Summary—Eighty-eight urinary tract stone formers (74 men) with idiopathic hypercalciuria were treated by dietary calcium restriction alone. Short-term control of hypercalciuria was achieved in only 27 patients and all but 12 eventually escaped control. Failure of control was twice as likely in patients with severe hypercalciuria.

Almost all patients lived in a hard water area. In such areas at least, attempts to control hypercalciuria by diet alone are likely to fail and early introduction of additional treatment is advisable. In most severe hypercalciurics, such treatment should be introduced from the start.

Idiopathic hypercalciuria is commonly associated with recurrent urinary tract stone formation (Flocks, 1939; Rose and Harrison, 1974), the hypercalciuria being widely believed to predispose to the development of stones. Understandably, therefore, attempts at prophylaxis have been aimed in the main at reducing urinary calcium excretion. Dietary calcium restriction and treatment with thiazides or sodium cellulose phosphate are most frequently employed.

Dietary calcium restriction has the merit of simplicity and freedom from drug-induced side effects. Since hypercalciuria is a consequence of increased gastrointestinal calcium absorption in most, if not all patients, it is also logical treatment. For these reasons, dietary restriction alone is often the first prophylactic measure to be introduced. Unfortunately, we find in clinical practice in a hard water area that dietary control of hypercalciuria is seldom achieved.

Patients and Methods

Two hundred and two urinary tract stone formers were referred to the Stone Clinic at St Bartholomew's Hospital between 1971 and 1975 for metabolic investigation. One hundred and thirty-four (66%) were found to have idiopathic hypercalciuria, defined as a mean of 2 or more urinary calcium measurements greater than 7.5 mmol/24 h in men and greater than 6.25 mmol/24 h in women. Hyperparathyroidism and other causes of hypercalciuria were excluded.

All urine measurements were made on outpatients taking a normal diet, urine being collected in vessels containing 15 ml of 6M HCl. Two consecutive collections were made and patients were given written instructions to increase the accuracy of collections. Almost all lived in East London and Essex, both of which are hard water areas (mean tap water calcium concentration in 14 patients randomly investigated 2.6 mmol/l, range 2.1 to 3.3 mmol/l). Urine calcium concentration was measured with a Perkin-Elmer 30 Atomic Absorption Spectrophotometer.

Of 134 patients with idiopathic hypercalciuria, 88 (74 male) were suitable for study. Twenty-five patients were treated with sodium cellulose phosphate or a thiazide *ab initio*. Seventeen patients failed to attend again after the diagnosis had been made and 4 declined treatment after discussion.

In 58 patients, daily dietary calcium intake was assessed on detailed questioning by a qualified dietician. Verbal and written instruction in a diet containing less than 10 mmol of calcium in food daily was given to all 88 patients. The exact degree of dietary calcium restriction was agreed by discussion between patient and dietician. Most patients agreed to take 7.5 to 8.75 mmol calcium daily. Patients were advised to maintain a high fluid intake. Dietary sodium and oxalate were not restricted.

After starting the diet, urinary calcium measurements were repeated within 1 to 3 months. Short-term control was defined as a fall in urinary calcium excretion (mean of two 24-h measurements) to less than 6.25 mmol/24 h in men and to less than 5.0 mmol/24 h in women. Urinary

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calcium measurements were made every 2 to 6 months after this initial assessment and have been examined to determine the number of patients who later escaped control (*vide infra*). Duration of follow-up ranged from 2 months to 5 years.

Domestic water softeners (Permutit) were supplied to 9 patients who were not controlled by diet alone.

Statistical analysis of results was by student's t-test for paired or unpaired data as appropriate.

Results

Results are expressed throughout as mean ± standard deviation (Fig.). Of the 88 patients, 74 were men (mean age 42 years) and 14 women (mean age 50 years). Overall pre-treatment urinary calcium was 10.0 ± 2.3 mmol/24 h, being 10.2 ± 2.3 in men and 9.1 ± 1.7 in women. Overall urinary calcium on diet was 7.9 ± 2.8 mmol/24 h, being 8.2 ± 2.9 in men and 6.3 ± 2.0 in women. In both men and women, urine calcium excretion/24 h was significantly reduced on diet ($P<0.001$). Twenty-three (30%) of the men and 4 (25%) of the women were controlled by diet. Pre-treatment urinary calcium in those patients who were controlled was significantly lower than in those remaining uncontrolled (9.1 ± 1.9 v 10.4 ± 2.3, $P<0.02$). Of 51 men with urine calcium >8.75 mmol/24 h, 10 were controlled on diet, in contrast to 13 of 23 men with urine calcium excretion below 8.75 mmol/24 h. This difference is significant ($P<0.005$). Mean percentage fall in urine calcium was identical (20%) in patients with severe (>8.75 mmol/24 h) and less severe (<8.75 mmol/24 h) hypercalciuria.

Mean daily dietary calcium intake recorded in 58 patients was 36 mmol (49 men, 36.9 mmol; 9 women, 31.0 mmol). There was no significant difference in initial calcium intake between the controlled and uncontrolled groups.

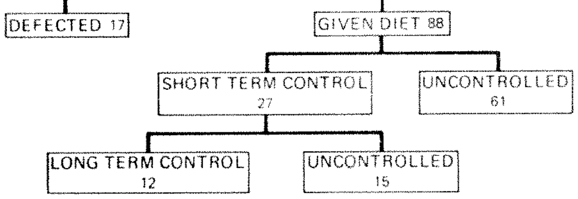

Fig. Outcome of attempted control of hypercalciuria.

On follow-up, all but 12 patients escaped from control, the mean of 2 or more measurements of 24-h calcium excretion exceeding 6.25 mmol in men and 5.0 mmol in women.

Escape from control typically occurred within 12 months of commencing the diet. The majority of "long-term controlled" patients have been followed for longer than 12 months.

In 9 patients, urinary calcium before a domestic water softener was used was 7.9 ± 1.95 mmol/24 h. Urinary calcium with the softener was 6.5 ± 1.8 mmol/24 h. This reduction did not achieve statistical significance ($0.10>P>0.05$). Three of the 9 patients were brought into the controlled range.

Mean 24-h urine volume measured on 200 occasions in 15 out-patients instructed to maintain a high fluid intake was 1860 ml. Given a mean tap water calcium of 2.6 mmol/l, water intake would account for a mean daily additional calcium intake of 4.8 mmol.

Discussion

No treatment is of proven value in reducing the increased risk of stone formation in idiopathic hypercalciuria since prospective, adequately controlled studies are lacking. Though falling short of formal proof, the results of treatment with thiazides are highly suggestive of benefit (Yendt *et al.*, 1970); encouraging early results with sodium cellulose phosphate have also been reported (Pak *et al.*, 1974). Both of these agents reduce urinary calcium excretion and it is reasonable to suppose (though in the case of thiazides, especially, open to question) that benefit, if any, derives from this action. It is thus reasonable current practice to attempt to correct hypercalciuria in recurrent stone formers.

Our definitions of hypercalciuria and adequate control are open to debate. We have taken the upper limit of normal urinary calcium to be that recommended by Hodgkinson and Pyrah (1958) and have attempted to reduce urinary calcium to well within their normal range. Some authors suggest that higher upper limits for normal urinary calcium excretion should be accepted (Rose and Harrison, 1974; Watson and Dale, 1966). The observations of Watson and Dale on out-patients in London are particularly convincing in this regard. It is self-evident that less stringent definitions of "hypercalciuria" and of "control" would exclude some of the patients we have studied from consideration and would also increase the percentage regarded as being satisfactorily treated. We regard our definitions as reasonable in the present state of knowledge. If this be accepted, only 12 out of 88 patients (14%) were controlled in the long term. If the 17 patients who failed to attend follow-up are considered to be treatment failures and are included in the assessment of results, only 11% of patients were controlled.

A major factor in failure of dietary treatment was non-compliance: out-patients on the diet typically admitted to breaking it or were found to be doing so on assessment by a dietician. Almost all patients complained that restriction of dairy products and normal bread was irksome. Motivation to adhere to the diet was often weak as most patients were symptom-free for most of the time.

A possible further reason for the relative failure of diet was the additional calcium load provided by drinking water in patients advised to maintain a high fluid intake. The provision of a water softener markedly reduced urine calcium in a few patients, but the majority remained uncontrolled. This additional measure seems worthy of trial in those whose main source of drinking water is domestic.

It is unlikely that even more rigid dietary calcium restriction than we have attempted would be acceptable to more than the occasional patient. Diets aiming to restrict calcium intake below 5 mmol/day—and therefore eliminating milk and normal bread entirely, as well as restricting some vegetables—are practicable only for the occasional dedicated individual such as the patient described by Dent and Watson (1965).

We conclude that mild hypercalciurics will frequently need additional treatment, such as a thiazide diuretic or sodium cellulose phosphate, and that severe hypercalciurics should receive such treatment from the start.

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Urological Complications in 119 Consecutive Renal Transplants

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Summary—One hundred and nine patients undergoing 119 transplants have been followed up from 8 months to 9 years. Urological complications occurred in 16 transplants, an incidence of 13.4%.

Ureteroneocystostomy was performed primarily in all cases; in 98 by the conventional Politano-Leadbetter technique with 9 (9.2%) urological complications and in 32 by an extravesical technique with 7 (21.8%) urological complications.

One patient died as a result of ureteric obstruction, without operation. In 3 patients with lower ureteric obstruction, transurethral ureteric meatotomy was successful in 2 cases and resulted in no change in renal function in the third.

Two patients with urinary fistulae were managed successfully by continuous drainage with indwelling urethral catheters. The remaining 10 patients required 12 open surgical procedures for relief of ureteric obstruction, with improvement in function in 7 patients.

Urological complications following renal transplantation are all potentially serious as the patients are on immunosuppressive therapy. This paper presents our experience with urological complications in 119 consecutive transplants from November 1968 to December 1977.

Patients and Methods

One hundred and nine patients received 119 transplants. Four grafts came from living related donors and 115 from cadavers. There were 8 second transplants and 2 third transplants. The initial warm ischaemia time for cadaver grafts varied from 2 to 80 min and the total ischaemia time from 159 to 1152 min. Bilateral nephrectomy was carried out on 77 of the recipients before transplantation. Azathioprine and steroids were used for immunosuppression and our regime has been fully described elsewhere (McGeown *et al.*, 1977).

Prior to commencing the operation the bladder was washed out with a 1% solution of neomycin through a Foley catheter. One hundred and fifty ml of 1% neomycin solution were left in the bladder and the catheter spigoted. After circulation was restored to the graft a ureteroneocystostomy was performed. In earlier cases (87 transplants) the technique of ureteroneocystostomy was similar to that described by Politano and Leadbetter (1958) without the use of a ureteric splint. Later in the series (32 transplants) an extravesical method of ureteroneocystostomy (MacKinnon *et al.*, 1968) was found to be simpler and less time-consuming than the former method and was carried out as follows.

The ureter was trimmed to the length required to reach the lateral wall of the bladder without undue laxity or tension and ensuring that the blood supply to the ureter was adequate, as judged by fresh bleeding from its distal end. A vertical myotomy, 3 to 4 cm long, was made on the lateral wall of the bladder and the submucosal space opened over a distance of 1 cm on each side of the myotomy. A small incision in the mucosa at the distal end of the myotomy was made and the ureter anastomosed, after spatulation, to the bladder with 4 to 6 interrupted stitches of 4/0 chromic catgut through all layers of the ureter and the bladder mucosa. The end of the ureter was invaginated into the submucosal space and the edges of the myotomy approximated over the lower end of the ureter with interrupted 2/0 chromic catgut stitches.

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A Foley catheter was left in the bladder for 4 days if there was no urine excretion or for 7 to 10 days if there was early graft function.

When a small urinary leak occurred, the fluid was identified as urine by comparison with the blood and urinary urea levels, but usually the rapid increase in volume from the fistula made the diagnosis clear. The diagnosis of obstruction was usually suspected when a previously successful graft declined in function, especially if the patient remained clinically without symptoms. The absence of hypertension, lack of increase in protein excretion (although 2 patients with urinary obstruction also developed heavy proteinuria due to recurrence of mesangioproliferative glomerulonephritis of "dense deposit type") and urinary N-acetyl-beta-D-glucosamidase were helpful. Renography, high dose pyelography and, in those patients where the orifice of the new ureter proved accessible, ascending pyelography were used. As well as the appearance of the ureter at operation in the most recent 3 cases, transureteric pressure measurements were used as confirmatory evidence of obstruction. A kidney biopsy was carried out in all cases and the results of these will be the subject of a separate communication.

Results

In 119 transplants, urological complications occurred in 16 patients (Table), an incidence of 13.4%. One (E.S.) of these 16 patients died from a chest infection with failing graft function at 1 year, a mortality of 6.7% for urological complications.

Urinary Fistula

Six patients developed a urinary fistula. In 2 patients the fistula followed soon after operation and closed spontaneously after a period of urethral catheter drainage. In 1 patient the fistula occurred 19 days after transplantation and was due to necrosis of the ureter. The necrotic ureter was excised and using the patient's own ipsilateral ureter, a ureteroureterostomy was performed. In 3 patients the fistula followed reimplantation of the ureter for treatment of late stenosis. One was re-explored within 24 h and the anastomosis was reconstructed with an excellent result. In a second patient the fistula closed spontaneously after continuous bladder drainage for 3 weeks. In the third patient urine began to leak from the drainage tube on the fifth day and at operation on the seventh day the lower end of the ureter was found to be narrowed and non-viable. Viable ureter was reimplanted and a ureteric splint was left *in situ* for 14 days. The kidney function has improved considerably.

Table

Ureteroneocystostomy	*Number of cases*	*Ureteric problems*	%
Politano-Leadbetter	87	9	9.2
Extravesical technique	32	7	21.8
Total	119	16	13.4

Antibiotics were not used prophylactically. Two patients with urinary fistulae developed urinary infections and were treated with appropriate antibacterial therapy. Immunosuppressive therapy was continued uninterrupted in these patients.

Ureteric Obstruction

Thirteen patients were found to have ureteric obstruction between 3 months and 6 months after transplantation.

In 1 patient a tight stenosis was discovered at post mortem. The graft had functioned well at first but function gradually declined and the patient died from a chest infection 12 months after transplantation.

In 1 patient the lower 5 cm of the ureter were stenosed and the remaining upper ureter grossly dilated but too short for reimplantation with an antireflux procedure. The ureter was anastomosed directly to the dome of the bladder with a successful result.

In 3 patients the obstruction was due to stenosis of a short segment of the lower end of the ureter and transurethral ureteric meatotomy was sufficient for relief of the obstruction. Graft function improved in 2 patients but did not change in the third.

In 4 patients the obstruction was due to kinks in the ureter with periureteric fibrosis. In 1 patient the ureter was straightened by freeing it from the fibrous tissue, with a successful result. In the other 3 patients the kinked ureter was freed and then reimplanted, with successful results in 2; in the other patient the kidney was lost soon afterwards from irreversible rejection 6 months after transplantation. In another patient the ureter was twisted at the lower end and was reimplanted, developed a urinary leak, but reimplantation a second time was successful.

In 1 patient the obstruction was due to dense periureteric fibrosis and had been present for many months before operation. The ureter was freed by dissection but graft function has slowly declined over the following 9 months, although it continues to support life.

Two other patients developed stenosis of the lower end of the ureter. In one this was complicated by acute rejection 11 months after transplantation. The ureter was reimplanted and antirejection treatment given with some success, but graft function is declining 6 months later.

The remaining graft had 2 ureters which had been joined and anastomosed to the bladder as a singled ureter by the extravesical technique, where stenosis occurred. Both anastomoses were repeated, with a successful result.

Discussion

The incidence of urological complications in recently reported series has ranged from 4 to 30% and mortality rates attributed to these complications have ranged from 0 to 68% (Prout *et al.*, 1967; Martin *et al.*, 1969; Belzer *et al.*, 1970; Starzl *et al.*, 1970; Williams *et al.*, 1970; Robson and Calne, 1971; Weil *et al.*, 1971; O'Donoghue *et al.*, 1973; Donaldson *et al.*, 1977). In most of these series, the Politano-Leadbetter technique of ureteroneocystostomy was used. In 1 series of 35 transplants using the extravesical technique, only 1 urological complication was encountered (Woodruff *et al.*, 1969) and in another series of 50 transplants, 5 significant urological complications occurred (Clunie *et al.*, 1974).

It is generally accepted that the successful management of ureteric complication requires early diagnosis and surgical correction. In our series, in the case of a urinary fistula the decision to undertake surgical exploration was dictated by the severity of the leakage. It was deemed necessary in 3 cases, when all urine excreted by the graft was passed through the fistula, indicating ureteric necrosis (H.D.) or complete disruption of a ureterovesical anastomosis (E.D. and K.McI.). In the case of a urinary fistula with a proportion of urine excreted by the graft still passing through the bladder, indicating incomplete disruption of a ureterovesical anastomosis, we found that conservative treatment was successful so long as strict attention was paid to the prevention of infection.

On the other hand, we have found that better results were obtained in those cases of ureteric obstruction where the diagnosis was quickly followed by surgical correction of the obstruction. In patients with gradually deteriorating graft function due to ureteric obstruction, delay in surgical relief was accompanied by a less satisfactory result. In 1 patient (A.R.) whose graft function deteriorated over several months and was treated with antirejection therapy on 3 occasions with doubtful response, there was little improvement in graft function after relief of ureteric obstruction. Renal biopsy at the time of operation showed no signs of acute rejection and she still has a life-supporting graft 9 months after her latest operation. In 2 patients (J.W. and D.B.) with already deteriorating renal function, the result of ureteric obstruction which had been left untreated for some time, acute rejection supervened and resulted in a more rapid decline in renal function. J.W. had a graft nephrectomy for acute irreversible rejection shortly after reimplantation of the obstructed ureter. D.B. made a good recovery after repeat ureteroneocystostomy and antirejection therapy, but her serum creatinine has gradually increased and graft function is poor 6 months later. In our experience, ureteric obstruction is more common than late rejection and must always be considered when renal function deteriorates. In addition to clinical evaluation and standard tests of renal function, we made use of renography (Doherty *et al.*, 1978), high dose pyelography, ascending ureterography, urinary N-acetyl-beta-D-glucosamidase and urinary protein excretion, and sometimes renal biopsy to distinguish between ureteric obstruction and rejection. As well as assisting in the diagnosis, radiological investigations helped to define the site and extent of ureteric obstruction so that corrective surgery could be planned.

Transurethral meatotomy, a recommended procedure for the relief of ureteric obstruction, has been described previously (Donaldson *et al.*, 1977) and was successful in 2 of our patients. If, on intravenous pyelography, the stenosis is seen to be confined to the lower end of the ureter, cystoscopy should be performed and if this reveals stenosis confined to the tip of the ureter, the remainder of the ureter within the submucosal tunnel will be seen to be normal or dilated, making transurethral meatotomy a simple and effective procedure.

Emphasis should be placed upon prevention of urological complications with careful attention to technique. Ureteric necrosis is due to damage to the ureteric blood vessels and may occur during removal and handling of the kidney but may be unavoidable if the ureter has an anomalous blood supply mainly through arteries not arising from the renal artery or its branches. Ureteric obstruction due to kinking of the ureter and periureteric fibrosis could probably be avoided by ensuring that the ureter is just long enough to reach the bladder without undue tension.

In our series of 119 transplants the overall incidence of urological complications was 13.4%, with an incidence of 21.8% when the extravesical technique was used compared with 9.2% when the Politano-Leadbetter technique was used. Screening by renography has been carried out on most of the surviving grafts done by the Politano-Leadbetter technique (Doherty *et al.*, 1978) and it seems unlikely that more cases of obstruction will turn up in this group. Screening for signs of obstruction of the remaining grafts performed by the extravesical technique is planned. Renography and intravenous pyelography suggest obstruction in 2 further cases of the 5 already screened. In our hands the extravesical technique leads to a higher complication rate than the Politano-Leadbetter technique. We feel that the complication rate of the extravesical technique is so high that it would be unjustifiable to continue with its use and we have decided to return to the Politano-Leadbetter method of ureteroneocystostomy.

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Carcinoma of the Renal Pelvis Following the Abuse of Phenacetin-containing Analgesic Drugs

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Summary—Five cases of renal pelvic carcinoma are reported in female patients who abused phenacetin-containing analgesics.

The mechanism of carcinogenesis in analgesic abuse is discussed and epidemiological factors are considered.

The possibility of development of a renal pelvic tumour in patients with analgesic nephropathy is emphasised.

It is generally known that abuse of phenacetin-containing analgesic drugs can cause nephropathy (Prescott, 1975; Stewart and Gallery, 1976). However, little attention has been paid to the fact that patients with this kind of nephropathy also have an increased risk of developing a transitional cell carcinoma of the renal pelvis. Hultengren *et al.* (1965) were the first to report 6 cases of transitional cell carcinoma among 103 patients with papillary necrosis; in 5 of the 6 there was an association with the abuse of phenacetin-containing analgesics. Johansson *et al.* (1974) reviewed 62 cases in Sweden of phenacetin-induced uroepithelial tumours of the renal pelvis. To date about 130 cases have been reported in the literature (Landmann-Kolbert *et al.*, 1975; Storey *et al.*, 1977).

Since the beginning of 1975 we have paid special attention to patients with transitional cell carcinoma of the renal pelvis by investigating carefully, by means of personal interviews, the use of analgesic drugs containing phenacetin. Nine of 24 patients with a malignant tumour of the kidney had a transitional cell carcinoma of the renal pelvis and 5 of the 9 had taken approximately 5 to 15 kg phenacetin over a period of 10 years. All of these patients were female.

Case Reports

Case 1. A 39-year-old woman presented with a 6-month history of pain in the right loin and fever. On examination a mass was felt in the right upper abdomen. The urine was sterile on culture and contained a few white cells. Hb 7.9 mmol/l; leucocytes $13.7 \times 10^9/l$; ESR 50 mm; blood urea 8.1 mmol/l; serum creatinine 180 μmol/l; electrolytes were normal. Excretion urography showed no excretion by the right kidney. The left kidney showed papillary deformities. The right retrograde pyelogram showed a total obstruction at the pelviureteric junction. The provisional diagnosis was pyonephrosis of the right kidney. At operation an enlarged, inflamed kidney was found and removed.

Histological examination showed, unexpectedly, an undifferentiated transitional cell carcinoma of the renal pelvis. The tumour was infiltrating the perirenal tissue. No papillae were available for histological examination.

During the post-operative period the serum urea and creatinine values rose. The patient died at home from local recurrence and uraemia 5 months after nephrectomy. We learned from her husband that because of chronic headaches she had taken various analgesic drugs over the previous 13 years. The total ingested dose of phenacetin was estimated to be approximately 7 kg.

Case 2. A 45-year-old woman was admitted to the dialysis unit, having developed colicky pains in the right loin and macroscopic haematuria. In 1974 she had had a period of macroscopic haematuria and on 3 occasions had passed a piece of tissue on micturition following colicky pains. One of the pieces had been shown histologically to be a necrotic papilla. The urine was sterile on culture and contained many erythrocytes and leucocytes. HB 3.1 mmol/l; leucocytes $9.7 \times 10^9/l$; ESR 115 mm; blood urea 18 mmol/l; serum creatinine 786 μmol/l. An excretion urogram had shown bilateral diminution of the renal contours and signs suggestive of papillary necrosis. The right retrograde pyelogram showed a space-occupying lesion in the renal pelvis. At operation the kidney was enlarged. A tumour was infiltrating the

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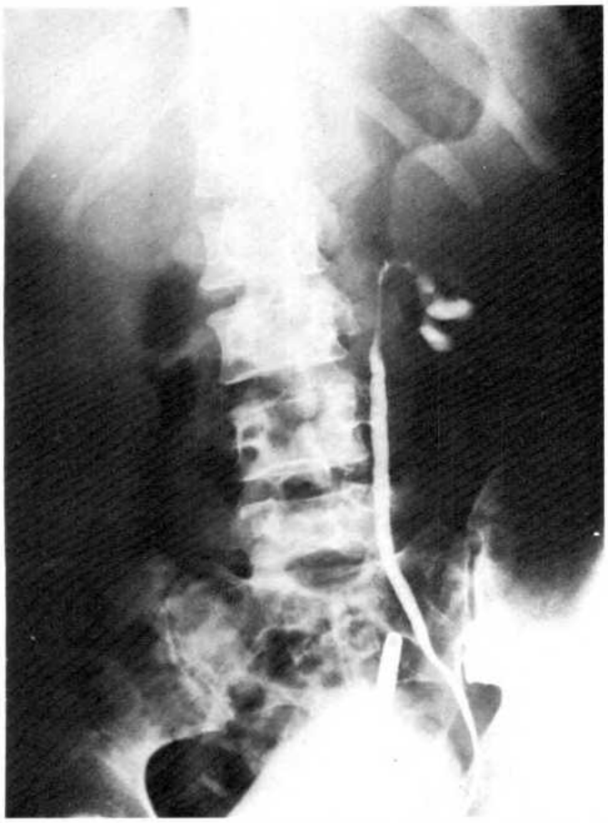

Fig. 1 Left retrograde pyelogram showing filling of the enlarged lower calices only.

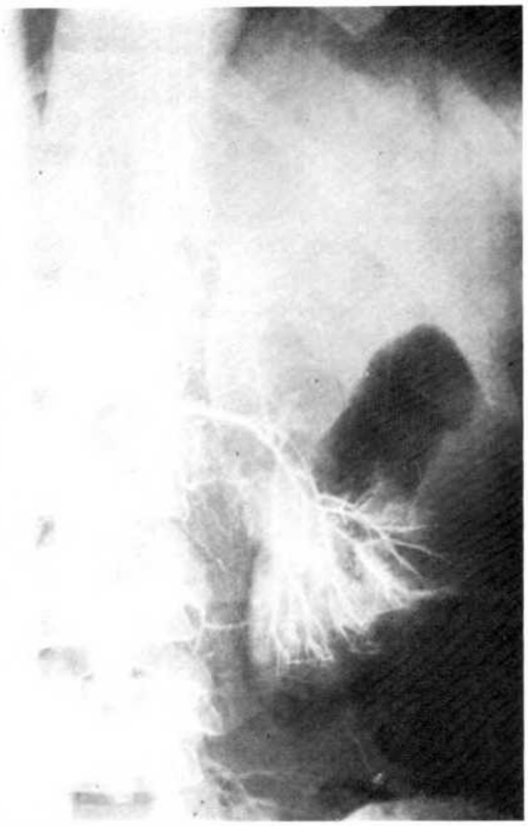

Fig. 2 Angiography of the left renal artery revealing an avascular space-occupying lesion in the upper part of the kidney.

perirenal tissue and the vena cava appeared to be involved. A palliative nephrectomy was carried out.

Histopathological examination showed an undifferentiated transitional cell carcinoma infiltrating the entire kidney. Papillary structures were hardly recognisable, confirming the radiological findings.

Post-operative dialysis was continued but the patient died at home 5 months later from a recurrence. She had taken huge amounts of phenacetin over the course of the previous 9 years for chronic headaches. We were unable to make an accurate estimate of the total dose.

Case 3. A 42-year-old woman was admitted with severe pain in the right loin, macroscopic haematuria, nocturia, loss of weight and pyrexia. Urine cultures revealed *Esch. coli* and enterococci. The sediment contained many erythrocytes and leucocytes. Cytological examination of the urine showed malignant cells class III (Bergkvist *et al.*, 1965). Hb 6.1 mmol/l; leucocytes $18.7 \times 10^9/l$; ESR 18 mm; blood urea 19.7 mmol/l; serum creatinine 281 µmol/l; electrolytes were normal. Excretion urography showed that the left kidney was enlarged because of a space-occupying lesion in the upper part of the kidney. The right kidney showed an even, shrunken contour, decreased excretion and papillary necrosis. A left retrograde pyelogram showed filling of the enlarged lower calices only (Fig. 1). Angiography of the left renal artery revealed an avascular space-occupying lesion in the upper part of the kidney (Fig. 2).

At operation a huge pyonephrosis with an infiltrating tumour was found and a palliative nephrectomy was carried out. Histopathological examination showed an undifferentiated carcinoma with localised squamous metaplasia (Fig. 3) and papillary necrosis (Fig. 4). Post-operatively the blood urea and creatinine values increased and shortly afterwards she died. It appeared that she had taken very large amounts of analgesic drugs, containing at least 10 kg phenacetin, for many years because of chronic headaches.

Case 4. A 73-year-old woman was admitted with macroscopic haematuria and pain in the right loin. One year previously analgesic nephropathy had been diagnosed, since when she had taken no more analgesics. She was being treated with methyldopa. She had taken large doses of analgesic drugs, containing at least 15 kg phenacetin, since the age of 19. The urine was sterile on culture and contained many erythrocytes. At urine cytology no malignant cells were found. Hb 7.9 mmol/l;

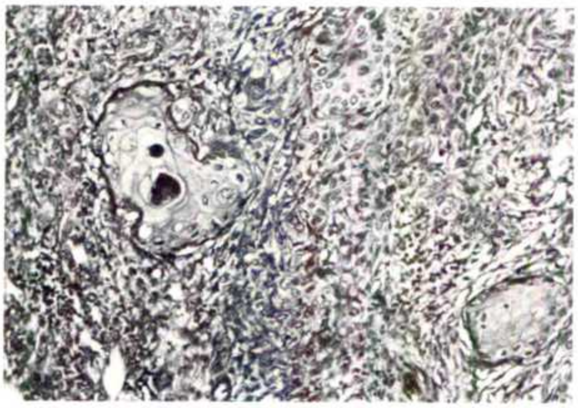

Fig. 3 Undifferentiated transitional cell carcinoma with localised squamous metaplasia. (H and E ×40).

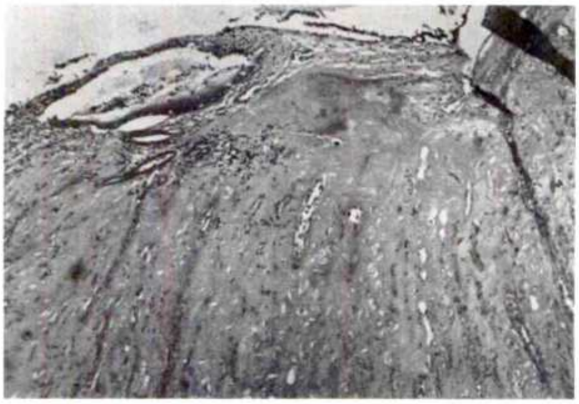

Fig. 4 Papillary necrosis. (H and E ×10).

leucocytes 6.0×10^9/l; ESR 18 mm; blood urea 11.3 mmol/l; serum creatinine 205 μmol/l; electrolytes were normal.

The excretion urogram showed no function on the right side. The kidney showed an even, diminished outline with signs of papillary necrosis. The right retrograde pyelogram showed a space-occupying lesion in the renal pelvis.

At operation a tumour was found which had infiltrated the surrounding tissues. The vena cava was involved. A palliative nephrectomy was performed. On histological examination an undifferentiated transitional cell carcinoma was found, extending into the perirenal tissue. There was papillary necrosis. Five months post-operatively the patient died with generalised bony metastases.

Case 5. A 72-year-old woman presented with periods of macroscopic haematuria over the course of the previous 6 months, on the last occasion with colicky pains in the right loin. The urine was sterile on culture and contained many erythrocytes. Cytology of the urine revealed malignant cells class IV (Bergkvist *et al.*, 1965). Hb 8.6 mmol/l; leucocytes 5.1×10^9/l; ESR 16 mm; blood urea 6.9 mmol/l; serum creatinine 79 μmol/l. The excretion urogram showed an irregular filling defect of the right renal pelvis and carcinoma was suspected. The left kidney was normal. At operation the diagnosis was confirmed. The tumour did not seem to infiltrate outside the kidney and nephroureterectomy was performed. Histopathological examination showed an undifferentiated transitional cell carcinoma infiltrating the perirenal fat. There was tumour growth in the lymphatics. The papillae appeared normal. Nine months after operation the patient is still in good health.

Since the age of 20 she had been taking large quantities of analgesic drugs for chronic headache and backache. The estimated amount of phenacetin was at least 5 kg. For many years she had also taken phenobarbitone.

Discussion

It would appear that there is a causal relationship between phenacetin in ingested analgesic mixtures and the development of carcinoma of the renal pelvis. Miller and Miller (1969) demonstrated in animal experiments that N-hydroxylation and esterification of the N-hydroxy group are possible activation steps in carcinogenesis by aromatic amines and amides. Nery (1971a) found that this applied to the aromatic amide phenacetin, as this drug is partly deacetylated in 4-phenetidine, whose metabolite is N-hydroxylated (N-hydroxy-4-phenetidine). Nery (1971b) identified, in the urine of phenacetin-treated rats, azoxy-4-ethoxybenzene, which is a condensation product of N-hydroxy-4-phenetidine or N-hydroxy-phenacetin. The excretion of 4-phenetidine and 2-hydroxy-4-phenetidine (a rearrangement product of N-hydroxy-4-phenetidine) in the urine of rats and man is dose dependent (Dubach and Raaflaub, 1969; Raaflaub and Dubach, 1969). With increasing doses of phenacetin these metabolites are excreted in the urine in increasing concentrations. Thus the concentration of N-hydroxy metabolites in the kidney could be a factor in carcinogenesis caused by phenacetin, as has been described for N-acetyl-paraminophenol (Napa, paracetamol) in the aetiology of papillary necrosis (Bluemle and Goldberg, 1968; Silberbusch, 1972).

Prescott (1969) found that patients taking barbiturates excrete a greater than normal proportion of a given dose of phenacetin as 2-hydroxy-metabolites. It is known that barbiturates, by increasing microsomal-drug metabolising enzyme activity in the liver, can modify the metabolism of certain drugs, phenacetin being one of them. In our fifth case this could have played a role. Little is known about the possible carcinogenic effects of the other components in analgesic mixtures.

It is remarkable that so many cases of renal pelvic carcinoma in patients who abuse analgesic drugs are reported from Sweden. Bengtsson and Angervall (1970) and Johansson *et al.* (1974) put forward a possible explanation. In 1961 phenacetin-containing preparations were put on prescription in Sweden. It is generally known that if analgesic abuse is discontinued in patients with analgesic nephropathy, renal function may remain stable or even improve (Gower, 1976). In the past, patients who continued to take phenacetin-containing analgesics died of uraemia before the induction time to develop a tumour was completed. The induction time (mean 22 years) exceeded the exposure time (mean 17 years) by an average of 5 years (Johansson *et al.*, 1974). As a result of the changed situation since 1961 many patients survive long enough for a carcinoma of the renal pelvis to develop.

Since 1953, when Spühler and Zollinger first described a chronic interstitial nephritis (often combined with papillary necrosis) in patients taking huge amounts of phenacetin, much attention has been paid to the condition. If affected patients survive longer as a result of ending drug abuse, more cases of pelvic carcinoma will be diagnosed. Bock and Hogrefe (1972) found, in a retrospective study of 31 cases of renal pelvic tumour, only one case with the combination of pelvic carcinoma and papillary necrosis in a patient who had abused phenacetin-containing analgesics. Bengtsson and Angervall's calculations in 1970, based on their study of 115 cases of analgesic nephropathy, suggested that more cases of renal pelvic carcinoma might have been expected. In 1973 Bock reported 5 cases (mean exposure time 19 years; mean induction time 21 years). It seems, therefore, that the first cases are being reported from Sweden as a result of phenacetin having been put on prescription in 1961. Three of our 5 patients had stopped taking phenacetin before a renal pelvic carcinoma was diagnosed (Cases 2, 4 and 5). Case 2 was admitted to a dialysis unit because of analgesic nephropathy with uraemia. In Case 5 there was no radiological or histopathological confirmation of papillary necrosis. Pre-existing nephropathy is not an absolute condition for the development of a renal pelvic tumour in analgesic abuse (Johansson *et al.*, 1974). Whatever the value of the hypothesis of Bengtsson and Angervall (1970) may be, it is clear that in every patient with known analgesic nephropathy who develops haematuria and/or pain in the loin, excretion pyelography and retrograde pyelography should be performed. Bengtsson *et al.* (1968), following up 104 patients with analgesic nephropathy over a mean period of 5.3 years, found 9 cases (about 8%) of renal pelvic carcinoma.

In most cases, renal pelvic carcinoma can be diagnosed by excretion and retrograde pyelography (Grabstald *et al.*, 1971; Williams and Mitchell, 1973; Johansson *et al.*, 1974). Selective angiography may be helpful in differentiating the condition from renal carcinoma. Diminished branching of arteries ("pruned tree" sign) is pathognomonic of a renal pelvic tumour; a small tumour, however, may not be shown. Pollen *et al.* (1975) described 6 patients with renal pelvic carcinoma in whom the diagnosis was confirmed by excretion and retrograde pyelography. Selective angiography was negative in 2 patients with small tumours.

Carcinoma of the renal pelvis in analgesic abuse tends to be less well differentiated (Bengtsson *et al.*, 1968). All of our cases showed undifferentiated transitional cell carcinoma; in Case 3 there was localised squamous metaplasia. Cytology of the urine can be an important aid in diagnosing carcinoma of the urothelium. Beyer-Boon (1977) found that if urine cytology in grade 2, 3 or 4 tumours (Bergkvist *et al.*, 1965) is frequently repeated, it proves to be a successful screening test in up to 98% of the cases. In the series of 62 patients studied by Johansson *et al.* (1974), urine cytology was performed in 12 cases with positive findings in 9. We found 2 positive results in 3 patients.

We conclude that it is important to be aware of the possibility that a urothelial tumour may develop in patients who abuse phenacetin-containing analgesic drugs and that urine cytology in such cases should be performed at regular intervals. If a malignant tumour of the pelvis is suspected, excretion and retrograde pyelography and urine cytology should be sufficient to establish the diagnosis.

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Transvaginal Milking of Lower Ureteric Stones into the Bladder

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Summary—In a selected group of adult female patients, stones in the lower ureter were transvaginally milked into the bladder.

The transvaginal milking of lower ureteric calculi into the bladder is easy and safe and is recommended in the poor surgical risk patient.

The surgical management of impacted calculi in the distal 3 to 4 cm of the ureter is problematic. The endoscopic extraction techniques, with basket or loop, have a success rate of only 65 to 90% (Constantian, 1974; Walsh, 1974; Henry and Tomlin, 1975). The abdominal approaches, whether retroperitoneal (Fox *et al.*, 1965), transperitoneal (Bose and Shaw, 1975), or transvesical (Maynard and Landsteiner, 1972; Barnhouse *et al.*, 1973), have their difficulties and complications, particularly in the obese patient or following previous pelvic surgery. In the adult female, the easy and adequate transvaginal surgical access to the lower ureter, described by Emmet in 1879, has recently been readvocated (O'Boyle and Gibbon, 1976). A ureteric stone palpable through the vaginal wall can occasionally be milked transvaginally into the bladder without surgery. We have used this technique in a selected group of patients.

Patients and Methods

Transvaginal milking of lower ureteric stones was performed in 7 patients in whom surgical intervention seemed to be hazardous because of cardiovascular disease or previous surgery to the ureter.

The patient is sedated with pethidine and Valium and placed in the lithotomy position. The bladder is emptied and the stone palpated bimanually through the anterolateral vaginal wall. It is then held between 2 fingers and moved downwards with repeated gentle milking movements. An endoscopic meatotomy may be necessary to allow passage of the stone through the ureteric orifice. The calculus is usually passed spontaneously through the urethra during the next few days.

Using the above technique, lower ureteric stones were manipulated into the bladder in 6 patients; in one patient the procedure was unsuccessful. The only complication encountered was a severe paralytic ileus in one patient, which responded to conservative treatment.

Case Reports

Case 1. A 76-year-old woman, known to have bilateral renal stone disease, was admitted to hospital with left renal colic and fever. She had previously had several ureterolithotomies on both sides. Excretory urography revealed bilateral renal calculi and an obstructing stone in the left lower ureter (Fig. 1). The stone was palpated through the anterolateral vaginal wall and milked down into the bladder. The patient was discharged from hospital 24 h later.

Case 2. A 34-year-old woman was admitted with left renal colic and fever. She had undergone left lower ureterolithotomy on 2 previous occasions. Excretory urography showed a stone in the lower pole of the left kidney and 3 others in the left lower ureter. The ureteric stones had caused obstruction and spontaneous extravasation of urine (Fig. 2). On vaginal examination the lowest stone was easily palpated and was gently milked down into the bladder. Within a few hours the patient passed the stone spontaneously through the urethra. The intensity of her flank pain and her temperature decreased subsequently. A plain film next morning showed that the proximal ureteric stones had moved downwards (Fig. 3). These stones were again palpated through the vagina and milked into the bladder. They were passed through the urethra the following day (Fig. 4). The patient was discharged 48 h later.

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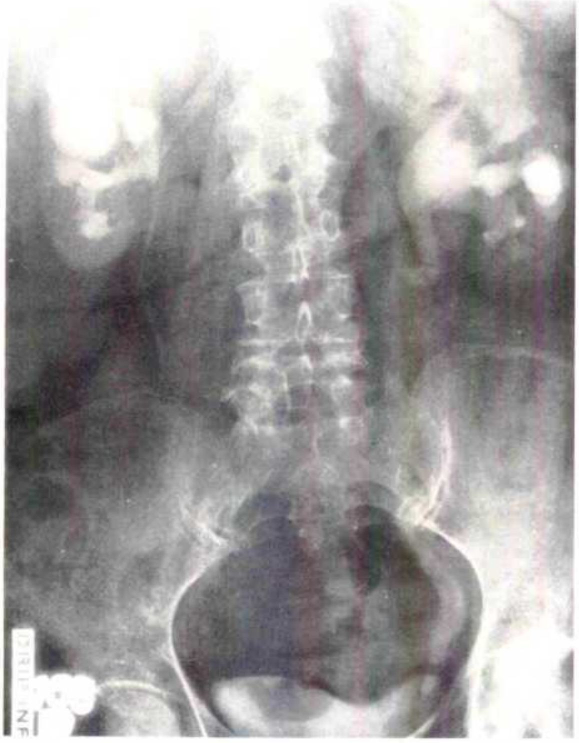

Fig. 1 Case 1. Drip infusion pyelogram showing the obstructing stone in the juxtavesical ureter.

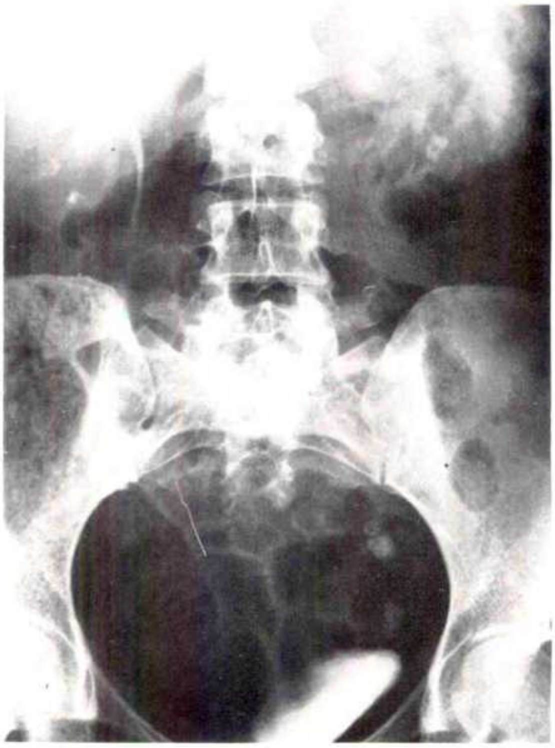

Fig. 2 Case 2. Intravenous pyelogram showing poorly functioning left kidney and spontaneous extravasation of contrast medium around it. One stone is seen in the lower pole of the kidney and 3 others are located in the distal ureter.

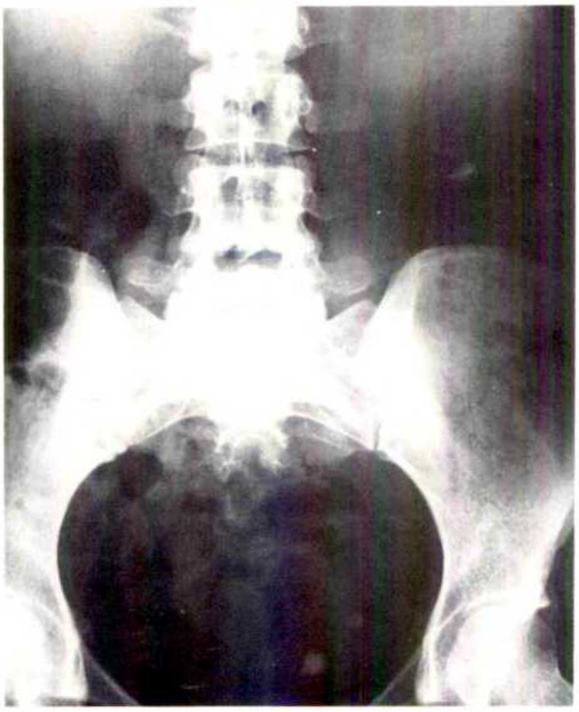

Fig. 3 Case 2. Plain film showing new, more distal location of the 2 remaining ureteric stones.

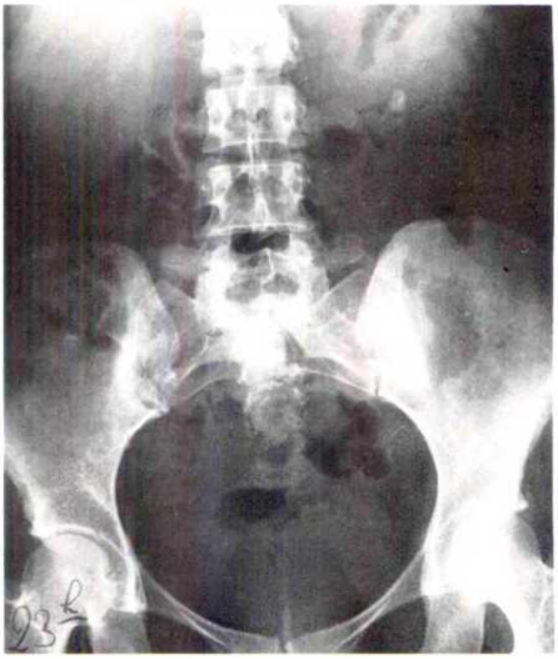

Fig. 4 Case 2. Plain film 23 h later. No stones are seen in the ureter or in the bladder.

Case 3. A 72-year-old woman was admitted to hospital with right renal colic and fever. She had suffered a myocardial infarction 5 weeks before the present admission. Excretory urography showed an obstructing stone in the right lower ureter and spontaneous urinary extravasation around the right kidney (Figs. 5a and b). The stone was palpated through the anterolateral vaginal wall and milked down into the bladder. The patient left the hospital 48 h later.

Discussion

The success rate of the transvaginal milking procedure is no lower than that of the various methods of endoscopic stone extraction. Compared with the 2 to 10% incidence of complications encountered by extraction (Mahon and Waters, 1973; Grob and Bandhauser, 1974; Marquardt and Nagel, 1974; Walsh, 1974; Navratil and Grasset, 1975; Wolff *et al.*, 1975) and the 3 to 4% by ureterolithotomy (Fox *et al.*, 1965), the method is a very safe way of dealing with lower ureteric stones.

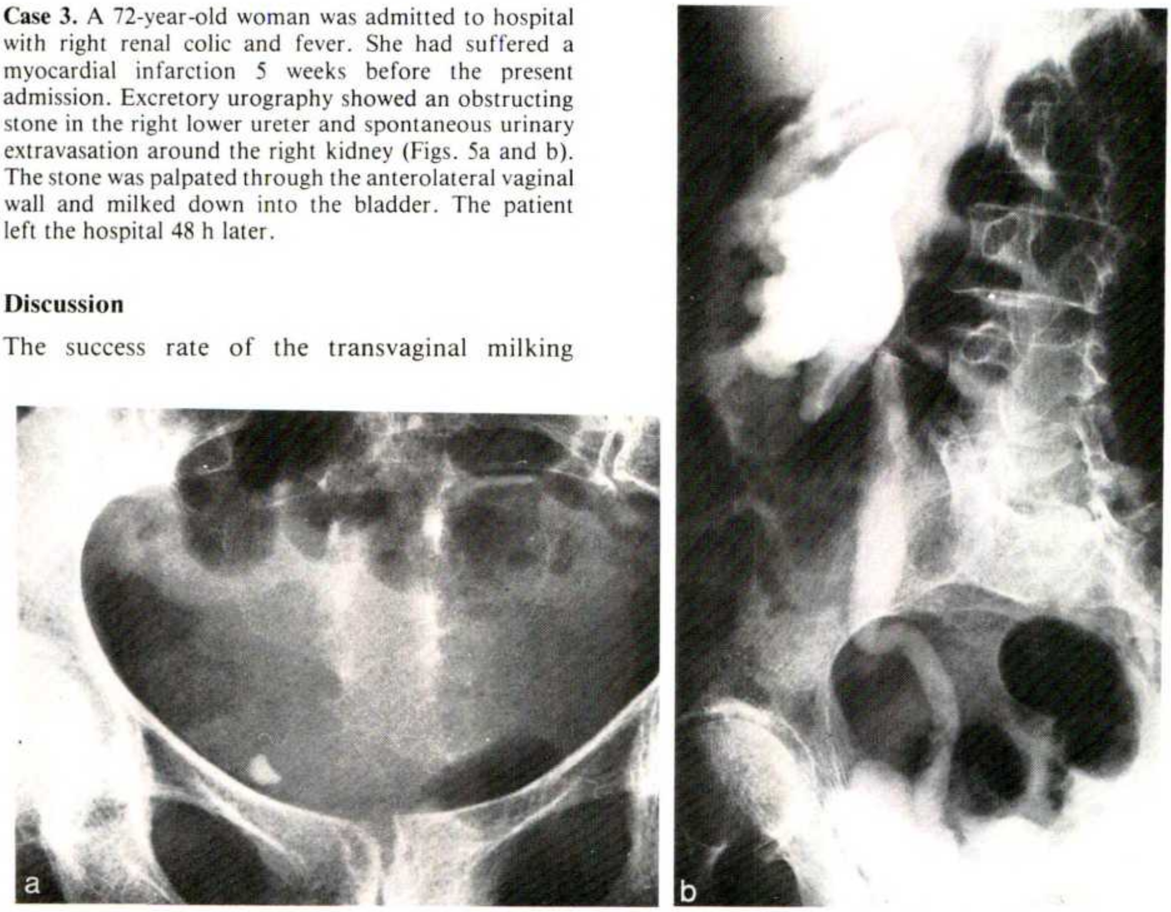

Fig. 5 (a) Case 3. Plain film of the pelvis, showing stone in the lower right ureter. (b) Case 3. Intravenous pyelogram, oblique exposure, showing obstructing stone in the juxtavesical ureter. Spontaneous extravasation of contrast medium around the right kidney.

We recommend the removal of lower ureteric calculi by transvaginal milking, especially in the poor risk patient.

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A Trial of Prophylactic Radiotherapy for Non-infiltrating Bladder Tumours

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Summary—In a series of 56 cases of non-invasive bladder tumours there was a 61.8% recurrence rate after endoscopic treatment.

In 29 cases a trial of prophylactic, very low dose (750 rad) radiotherapy was given; this was administered within a few days of the primary treatment. Twenty-seven cases received no radiotherapy.

Over follow-up periods of 2 to 5 years there were recurrences in 12 of the irradiated group compared with 11 out of the 27 controls.

Transitional cell non-infiltrating papillary tumours of the bladder recur in about half of the cases after the primary treatment. This presents a major problem that has not been solved. On the assumption that recurrences are due to the continued action of the original carcinogenic factors, the obvious solution would be to eliminate those factors. Although our knowledge of aetiology has extended in recent years, however, it has not reached the stage of successful clinical application. It might be possible to prevent recurrence by the use of an anti-tumour influence at a time when new tumours were at their earliest stage of development and therefore more frail and susceptible to injury. It might be that if the bladder were irradiated when potential tumours were in a very immature stage of development the tumour process could be aborted. The question arises—when do recurrent tumours begin to form?

It has long been suspected that a factor in the formation of recurrent tumours is the seeding or implantation in the bladder mucosa of cells detached from the primary tumour by the diathermy loop or electrode used in treatment (McDonald and Thorson, 1956). Hinman (1956) has suggested that trauma to the mucous membrane by the resectoscope sheath could facilitate implantation by causing abrasion of the mucosa. Recurrences that form in this way originate at the time of treatment and if they are to be prevented immediate action is necessary. Measures to this end have been practised for a long time but mostly without much success.

The composition of the irrigating fluid used in endoscopic treatment has been suggested as a factor in the formation of recurrent tumours. For example, there is some evidence that water (as opposed to isotonic fluids) is lethal to detached tumour cells because of osmotic factors. Isotonic (or nearly isotonic) solutions are widely used nowadays for endoscopic resection, but no figures have been published to show that they increase the incidence of recurrent tumours. In the series to be reported here, glycine was used in the primary treatment of all cases and also in those cases with secondary tumours treated as in-patients. In out-patients, water was used for cystodiathermy.

Instilling cytotoxic drugs immediately after endoscopic diathermy has some fundamental weaknesses and some dangers. If the drug is instilled into the empty bladder in optimum concentration it can only act in that strength for a short time because dilution commences at once with the inflow of urine from the ureters. Also side effects may be tiresome (for example irritation, particularly with Clorpactin) or serious. Abbassian and Wallace (1966) reported 2 deaths in 13 cases of intravesical Thiotepa due to agranulocytosis, and in many of the cases there had been a fall in the white count often sufficient to interrupt or stop the course. Serious systemic effects are probably diminished by delaying the application until the open mucosal wounds and hyperaemia have healed and settled, but this delay

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may mean that the critical opportunity has passed if one is aiming at the destruction of tumour seeds or at inhibiting the earliest stages of a tumour-forming process. This method, as it has been applied to established recurrences, involves repeated instillations.

Prophylactic very low dose irradiation has few of these disadvantages and is "non-invasive". A controlled trial was carried out on the following lines.

Patients and Methods

All patients seen between July 1967 and March 1970 with non-infiltrating transitional cell bladder tumours were entered for the trial provided that (i) the case had not been previously treated, (ii) the age of the patient was not under 50 for females or 35 for males, (iii) the cystoscopic and histological appearances were those of a benign tumour, *i.e.* non-infiltrating and well-differentiated, and (iv) there were no contraindications to irradiation.

The allocation of the patients to the control or the irradiation groups was made by random selection as soon as the histology report confirming non-invasion was available.

The original plan was to continue the trial for 3 years or until 100 patients had been entered. However, by the end of 3 years only 66 cases had been collected and no further cases were accepted after this as it appeared most unlikely that any significant result would emerge.

Of the total 66 cases entered for the trial 10 are excluded from the analysis: 7 due to insufficient follow-up, 1 because of a technical fault in entering her case, 1 because he refused the radiotherapy (after being entered for the trial) and 1 because a review of the histology suggested there might be infiltration. Of these excluded cases 6 were in the irradiated group and 4 were controls.

Thus 29 irradiated and 27 control cases were available for analysis (Table 1). The 2 series are closely comparable in respect of the important features (*e.g.* the primary growth was solitary in 18 of each group), although the controls were generally older and had a longer history of disease since the first symptom. In nearly two-thirds of the cases the primary tumour was solitary. The remaining cases were nearly equally divided between those with 2 or 3 tumours and those with 4 or more.

Table 1 Comparison of Groups

	Irradiated group	*Control group*
Total number of cases	29	27
Male	22	23
Female	7	4
Ages		
Under 50	5	0
50-69	20	20
70 and over	4	7
Length of history (weeks)		
Mean	22	34
Range	6-86	1-109
Primary findings		
Number of tumours		
1	18	18
2-3	5	4
4 or more	6	5
Length of follow-up		
2 years	4	6
3 years	8	7
4 years	9	10
5 years	8	4

Patients allocated to the group receiving irradiation were treated on the Cobalt^{60}Mobaltron, using an opposed anteroposterior pair of fields 10 × 10 cm at 70 cm source/skin distance. A central dose of 250 rad was given once weekly for 3 treatments to total minimum tumour dose of 750 rad in an overall time of 14 days. The very low dose was chosen arbitrarily so that should radiotherapy be necessary in the future for established invasive cancer, then this low dose would in no way prejudice the giving of a full dose at a later date.

The histology report was available 2 or 3 days after operation and the first application of radiotherapy was usually given within 24 h of that report, *i.e.* within 4 days of the endoscopic treatment.

All cases were followed up for a minimum of 2 years and over half of the patients in both groups were followed up for 4 years or more.

Results

All cases were followed up by periodic cystoscopy. The examination was done at 3-monthly intervals and then if there were no recurrences the interval was rapidly lengthened to 1 year and there maintained indefinitely. Minor recurrences (up to about 3 small tumours) were treated by cystodiathermy in out-patient clinics under

Table 2 Recurrences

	Irradiated group	*Control group*
Total number of cases	29	27
Without recurrence	11	11
With recurrence	18	16
Number of occasions on which recurrences were seen		
1	2	2
2 or 3	3	7
4 or more	12	7
Highest number of recurrent tumours seen on any one occasion		
1	3	2
2 or 3	8	9
4 or more	7	5

general anaesthesia. Larger or more numerous recurrences were admitted for either cystodiathermy or endoscopic resection.

In 3 patients (who all happened to be in the control group) additional forms of treatment were given. Two received 1 course of intravesical Thiotepa each (2 years and 2½ years after primary treatment). The third patient received 2 courses of Epodyl 4½ years after primary treatment, and as this was ineffective cystectomy was done.

The number of patients with recurrences was almost identical in the 2 groups (Table 2). The *frequency* of recurrence (as judged by the number of occasions on which recurrences were seen in any 1 patient) was slightly greater in the irradiated group; this was possibly owing to the slightly longer average follow-up period. The severity (as judged by the greatest number of tumours seen at any one time) was similar in the 2 groups.

Discussion

If a high or tumour-lethal dose of irradiation had been used instead of the very low dose of 750 rad then the outcome of the trial might well have been different. However, it was not considered justified to give such a high dose with all its attendant dangers in the treatment of histologically both non-malignant and non-invasive disease.

In addition, should the patient later have developed invasive carcinoma requiring radiotherapy a further radical course of treatment could not have been given.

There was no evidence that irradiation did anything to reduce the number or severity of recurrences (which alone would justify its use clinically) but it would need a much larger series to demonstrate this conclusively.

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Addendum

Since this trial was completed Burnand *et al.* (1976) have published the results of a series of cases in which a single instillation of Thiotepa was made into the bladder immediately after the primary treatment. Comparison with their control series showed that this prophylaxis with Thiotepa led to significantly fewer recurrences and there was virtually no trouble with systemic intoxication.

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Primary Vesical Sensory Urgency. A Clinical Trial of Bromocriptine

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Summary—A randomised double blind crossover trial of Bromocriptine against an inert placebo was performed in 14 patients with primary sensory urgency.

Bromocriptine was found to have no therapeutic advantage for these patients and the possible explanations for this finding are discussed.

"Although the sensation of vesical distension in mild degree comes at some time within everyday general experience, and that of more severe distension comes at some time within the notice of most individuals, these sensations are unusually difficult to describe in detail" (Denny-Brown and Robertson, 1933).

Normal awareness of bladder distension is peculiarly difficult to describe and may be referred to as pressure in the perineum, suprapubic fullness, suprapubic aching or definite pain. Each forewarns that voiding is imminent, is not associated with detrusor contraction in normal circumstances and is relieved as soon as micturition occurs.

The sensation of imminent voiding, manifest as the symptom of urgency and often associated with frequency and nocturia, may be produced by a wide spectrum of urological disease including cystitis, outflow tract obstruction, neoplasia, vesical stone and neurological disorders. Similar symptoms may also accompany some psychosomatic illnesses. It is usually possible to reach an accurate diagnosis by careful general and urological examination, and appropriate treatment results in resolution of symptoms. In a small number of patients, urodynamic investigations will demonstrate detrusor instability as a cause of persistent symptoms.

There are, however, patients who have identical symptoms of urgency and frequency who have no detectable organic urinary pathology and in whom the bladder is stable. These patients appear to appreciate bladder filling at pathologically small volumes, experience severe distension prematurely and seek relief by voiding at frequent intervals. This syndrome of primary sensory urgency is particularly refractory to treatment.

A report on the use of Bromocriptine (Sandoz) in the treatment of the unstable bladder drew our attention to the fact that while symptomatic relief was noticed by patients taking this preparation, bladder instability was not abolished (Farrar and Osborne, 1976).

It seemed possible that the drug may have been exerting an effect on bladder sensation either centrally or at a peripheral level, and that Bromocriptine may therefore be appropriate therapy for patients with primary sensory urgency.

A randomised, double blind crossover clinical trial of Bromocriptine against an inert placebo was therefore undertaken to assess any therapeutic effect of Bromocriptine on primary sensory urgency.

Patients and Methods

Twenty-one patients were fully investigated urologically by urine culture, chlamydial culture, exfoliative cytology, urography and endoscopy with mucosal biopsy where relevant, to exclude urinary tract pathology and in particular interstitial cystitis, chronic inflammatory and neoplastic disease. There were no coincident signs or symptoms of neurological disease which would account for the urinary symptoms. In each case the diurnal voiding frequency was less than 1½ h, and the desire to void accompanied by disagreeable urgency. Sixteen of these patients accepted a place on the trial but 2 were excluded, one because of a history of persistent dyspepsia

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and the other because of generalised arteriosclerosis.

Standard pressure flow videocystourethrography was performed in every case. The urodynamic findings were relatively constant. Each patient was able to refrain from voiding for 3 h prior to the study. The initial flow rate was normal. The filling cystometrogram showed immediate appreciation of bladder filling and at no time did the detrusor pressure exceed 10 cm H_2O, nor did the bladder outline appear abnormal during screening. On attempting to void there was often a delay in initiation of a detrusor voiding reflex despite intense urgency. Voiding occurred at normal flow rates and normal detrusor pressure.

Bromocriptine 2.5 mg tablets and identical inert placebo tablets were supplied in accordance with a randomised code prepared by the pharmacy department. Each drug treatment period lasted for 4 weeks with a one-week "washout" between. Each patient was given a progressive dosage schedule to a maximum of 7.5 mg of active substance daily.

Patients were seen at the start, at 4 weeks, 5 weeks and 9 weeks. At each visit urinary symptoms were recorded, as were any side effects. Flow rates were measured and blood taken for serum prolactin estimation.

At the end of each treatment period patients were asked to comment on the efficacy of the drug, and at the end of the 9-week period to comment on which preparation they considered more effective.

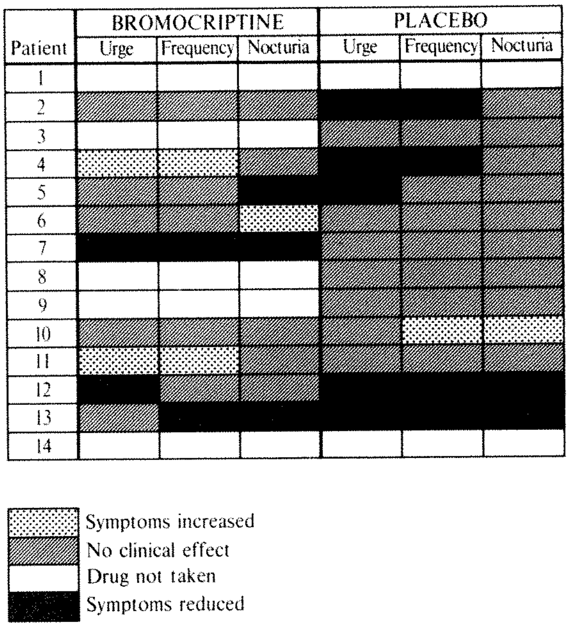
Results

Nine of the 14 patients in this study completed the trial. Five patients withdrew, 3 since they felt that the trial protocol and dosage schedule were "too much trouble" and 2 because of severe side effects of therapy—in both cases produced by the placebo.

The results are shown in the figure and the table.

Discussion

The syndrome of sensory urgency appears to be a distinct clinical entity. The diagnosis, however, can be made with confidence only after a full urological and urodynamic investigation to exclude alternative organic pathology.



Patient	BROMOCRIPTINE			PLACEBO		
	Urge	Frequency	Nocturia	Urge	Frequency	Nocturia
1	□	□	□	□	□	□
2	▨	▨	▨	■	■	▨
3	□	□	□	▨	▨	▨
4	░	░	▨	■	■	▨
5	▨	▨	■	■	▨	▨
6	▨	▨	░	▨	▨	▨
7	■	■	■	▨	▨	▨
8	□	□	□	▨	▨	▨
9	□	□	□	▨	▨	▨
10	▨	▨	▨	▨	░	░
11	░	░	▨	▨	▨	▨
12	■	▨	▨	■	■	■
13	▨	■	■	■	■	■
14	□	□	□	□	□	□

░ Symptoms increased
▨ No clinical effect
□ Drug not taken
■ Symptoms reduced

Fig. Clinical evaluation.

The patients in this series demonstrated several interesting characteristics. While their lives were often seriously disrupted by their bladder symptoms, particularly by distressing urgency and diurnal frequency, all managed to refrain from voiding for 3 h prior to the urodynamic investigation. This is in contrast to patients with detrusor instability, who are usually unable to comply with this request, and agrees with observations made by Hafner *et al.* (1977). In each case the desire to void was consistently appreciated at an abnormally low volume during the bladder filling phase, which indicates that the patients have increased bladder sensory perception. Finally, nocturia (Table), a symptom generally accepted as indicative of organic urinary pathology, was noted with only one exception.

It would seem therefore that an abnormality of bladder appreciation does occur in patients with this syndrome, though at present there is no effective drug treatment to alleviate their symptoms.

Theoretically a dopamine agonist preparation could produce an alteration in bladder proprioception which would account for the symptomatic relief noted in the unstable bladder syndromes (Farrar and Osborne, 1976). This may be brought about either by a central facilitation of the inhibitory centres or, conversely, by an inhibition of

Table Side Effects

Patient	*Nocturia*	*Bromocriptine*	*Placebo*	*Bromocriptine effect on prolactin level*	*Drug considered more effective by patient*
1*	3	–	–	–	–
2	3	Nil	Impotence	Nil	Placebo
3*	1	–	Nil	–	–
4	2	Nil	Nil	Reduced	Placebo
5	2	Headache, nausea	Periods earlier and longer	Nil	Placebo
6	2	Nausea	Nil	Increased	Placebo
7†	1	Period late	Nil	Reduced	Bromocriptine
8*	2	–	Depression, fatigue	–	–
9*	0	–	Headache, nausea, constipation, skin rashes	–	–
10	4	Headache, nausea	Nil	Nil	Bromocriptine
11	1	Nil	Nil	Nil	Placebo
12	1	Tired, stuffiness	Headache, depression	Reduced	Placebo
13	4	Tired, depressed	Breast tenderness	Reduced	Placebo
14*	2	–	–	–	–

* Patient withdrew from trial.
† Patient had chlamydial infection. Treated. Cured.

the facilitatory centres. Alternatively, a peripheral action may be responsible.

The results of this study, however, show that Bromocriptine has no therapeutic advantage over an inert placebo in patients with sensory urgency and there was no evidence of either a central or a peripheral effect of the drug on bladder function. These conclusions were based upon the assessment of subjective responses by the patient and the objective measurement of urinary flow rates which remained unaltered. A reduction in flow rate might be anticipated by a sympatheticomimetic action of the drug on the alpha-adrenergically innervated smooth muscle of the urethra, or by beta-inhibition of the detrusor.

It was of interest to note that the only patient to record a significant symptomatic response to Bromocriptine and who was unaffected by the placebo (patient 7, see Table) had organic pathology and was ultimately cured of chlamydial urethritis by appropriate antitrachomal therapy.

The lack of response in the other participants in the trial may be due to Bromocriptine being ineffective in a purely sensory condition or due to the dose being too low to produce a significant clinical response. In Parkinson's disease, for example, the drug has been used in excess of 300 mg per day to produce effective control. A further distinct possibility in this trial is that the patients may not have taken the tablets as instructed, since the anticipated decrease of the serum prolactin level was not observed in several patients receiving the active substance (Table). Hafner *et al.* (1977) point out that there are some patients who prefer to retain their symptoms of frequency and urgency and are resistant to any form of treatment. The poor attendance rate in some patients and the reluctance of others to try a new treatment may also be a reflection of this attitude.

There is undoubtedly a functional component in this syndrome, though whether this is the cause or effect of the symptomatology is difficult to establish. One patient who was excluded from the study showed remarkable insight and stated that her bladder symptoms were associated with periods of stress either at home or at work. Interestingly, she was not troubled by nocturia. Furthermore, the high incidence of side effects in those receiving the inert placebo would suggest a degree of introspection. These considerations support the opinion that the syndrome of primary sensory urgency may be of a psychosomatic nature (Jeffcoate and Francis, 1966; Frewen, 1972, 1976). However, the identical symptoms of each case, particularly the presence of nocturia in every patient, and the consistency of the urodynamic findings do suggest that there is some aberration of bladder sensation in this syndrome and that an alleviation of symptoms should be possible. Further studies on the effect of hydrostatic overdistension of the bladder, in an attempt to produce a sensory denervation, are in progress and will be reported in full in a future communication.

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Detrusor Instability following Surgery for Genuine Stress Incontinence

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Summary—Ninety-two female patients with genuine stress incontinence, and with otherwise normal bladder function, were treated by a colposuspension operation. Pre-operative and post-operative clinical and urodynamic assessments were performed on all patients. Following surgery 17 of them were found to have detrusor instability.

It is now widely accepted that incontinence due to a sphincter weakness alone (genuine stress incontinence) can, in the majority of cases, be cured by surgery, whereas that due to detrusor instability is resistant to surgery (Arnold *et al.*, 1973). Many operations exist for the correction of genuine stress incontinence and they may be divided into 2 broad categories: vaginal and suprapubic. Both types are commonly performed, although most of the reports available suggest that the cure rates achieved by a suprapubic approach are higher than those for vaginal surgery (Morgan, 1973). The colposuspension operation, first described by Burch (1961) has been shown to produce objective evidence of a cure in 88.6% of a group of 35 patients at 4 months post-operatively (Stanton *et al.*, 1976). The reasons for failure of this operation have been assessed (Stanton *et al.*, 1978) and include increased age, previous surgery for urinary incontinence, pre-operative symptoms of urgency and frequency, and detrusor instability.

Patients and Methods

Ninety-two patients attending the Urodynamic Clinic with a primary complaint of stress incontinence had a full history taken and underwent examination of their gynaecological, urological and neurological systems. A midstream specimen of urine was sent for culture and sensitivity and an independent peak flow rate was measured. Videocystourethrography (VCU) (Bates and Corney, 1971) was performed and a diagnosis of genuine stress incontinence (urethral sphincter dysfunction) was made if there was demonstrable stress incontinence in the absence of detrusor contractions and with a pressure rise of less than 15 cm of water during the provocative tests of fast bladder filling, coughing, passive posture change and catheter withdrawal. If neither stress incontinence nor detrusor instability was demonstrated on VCU a Urilos nappy test (Stanton and Ritchie, 1977) was performed. All patients with objective evidence of incontinence due to urethral sphincter dysfunction were treated by a modified colposuspension (Stanton *et al.*, 1976) preceded by a cystoscopy.

Two months after surgery all patients were re-assessed in the Urodynamic Clinic and a month later a further VCU and Urilos nappy test were performed. Thereafter all patients have been followed up annually by history, clinical examination and Urilos nappy test, and in those exhibiting post-operative detrusor instability a further VCU has been performed one year later. For the purposes of this study frequency is taken to be the passage of urine 7 or more times during the day or twice or more at night. The other definitions comply with the "Standardisation of terminology of lower urinary tract function" (International Continence Society, 1977).

Results

Ninety-two patients with genuine stress incontinence and stable bladders underwent a colposuspension operation. Post-operative urodynamic assessment showed that 75 (81.5%) had stable

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Table 1 Group 1 Patients Stable Post-operatively and Group 2 Patients Unstable Post-operatively

	Group 1 (75 patients)			*Group 2 (17 patients)*		
	Mean	*Range*	*SD*	*Mean*	*Range*	*SD*
Age	49.8	28-77	(11.4)	48.8	27-72	(12.6)
Parity	2.6	0-7	(1.8)	2.7	1-6	(1.4)
Previous operations for incontinence	0.7	0-3	(0.8)	1.2	0-3	(0.9)

bladders (Group 1) and 17 (18.5%) had unstable bladders (Group 2). The ages, parities and number of previous operations for incontinence are shown in Table 1.

Group 2 This was divided into 3 subgroups according to the VCU findings.

Group 2a Five patients with detrusor contractions greater than 15 cm of water during bladder filling (P1).

Group 2b Six patients with a pressure rise on standing (P2) greater than 15 cm of water without detrusor contractions. Five of these patients had a normal P1 rise—the other had a steep P1 rise of 30 cm of water.

Group 2c Six patients with a P1 rise greater than 15 cm of water without detrusor contractions with normal P2 rise.

Table 2 shows the pre-operative and post-operative clinical findings. The VCU results before and after surgery are shown in Table 3.

Twelve of the 17 patients with post-operative detrusor instability had a VCU performed a year later. Of these, 11 remained unstable but in some the type of instability had changed. The "cross-over" is shown in the figure.

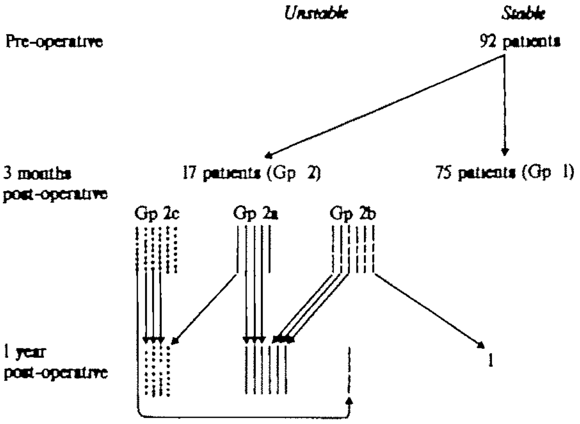

Fig. Change-over within the groups. All 92 patients underwent VCU pre-operatively and at 3 months post-operatively. Twelve of the 17 post-operatively unstable patients have been re-examined at one year

Discussion

In women, detrusor instability is an important cause of urinary incontinence as well as urgency and frequency of micturition. Although in the majority of cases detrusor instability is idiopathic, it may be due to an upper motor neurone lesion. In men, detrusor instability may be secondary to outflow obstruction and is often reversed by its relief (Turner-Warwick *et al.*, 1973). This reversal has not been observed in women (Farrar *et al.*, 1976) but outflow obstruction is rare in the female. The colposuspension is thought to produce continence by elevation of the bladder neck and possibly compression of the urethra. It would therefore seem reasonable to hypothesise that in our patients who have developed post-operative instability, excessive urethral compression has led to outflow obstruction and consequent detrusor instability. This is not the case, however, as one

Table 2 Pre-operative and Post-operative Clinical Findings

Symptoms and signs (% of patients)	*Group 1 (75)*		*Group 2 (17)*		*Group 2a (5)*		*Group 2b (6)*		*Group 2c (6)*	
	Pre-op.	*Post-op.*	*Pre-op.*	*Post-op.*	*Pre-op.*	*Post-op*	*Pre-op.*	*Post-op.*	*Pre-op.*	*Post-op*
Frequency										
Diurnal	61	36	70	35	60	60	66	50	100	0
Nocturnal	36	19	41	29	60	60	33	17	33	33
Urgency	61	33	76	64	40	80	100	66	66	50
Urge incontinence	51	19	70	47	40	60	83	50	66	50
Stress incontinence	100	16	100	29	100	20	100	33	100	50
Cystocoele	77	37	77	35	80	20	83	33	66	33

Figures in brackets represent number of patients in the group.

Table 3 Pre-operative and Post-operative VCU Findings

VCU	*Group 1 (75)*				*Group 2 (17)*				*Group 2a (5)*				*Group 2b (6)*				*Group 2c (6)*			
	Pre-op.		*Post-op*		*Pre-op*		*Post-op*		*Pre-op.*		*Post-op*		*Pre-op*		*Post-op*		*Pre-op*		*Post-op.*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Residual (ml)	5	(15)	49	(74)	23	(52)	33	(41)	13	(30)	28	(44)	33	(82)	10	(15)	21	(37)	57	(50)
First sensation (ml)	242	(97)	244	(92)	190	(48)	200	(70)	206	(25)	234	(50)	178	(69)	156	(74)	188	(43)	216	(68)
Capacity (ml)	497	(105)	488	(88)	493	(74)	463	(72)	460	(65)	430	(72)	535	(97)	514	(56)	479	(40)	438	(63)
PR_1 (pressure rise on filling) (cm H_2O)	4.3	(4.1)	5.1	(3.8)	6.7	(5.7)	17.1	(10.7)	7.6	(6.8)	24.8	(5.2)	5.2	(6.7)	4.7	(3.9)	7.6	(4.1)	23.0	(6.7)
PR_2 (pressure rise on standing) (cm H_2O)	3.5	(4.1)	3.2	(3.9)	3.6	(3.9)	14.0	(11.5)	5.6	(5.2)	11.0	(15.2)	4.5	(3.4)	22.8	(5.4)	0.9	(1.5)	7.8	(7.9)
Maximum voiding pressure (cm H_2O)	32	(16)	40	(18)	38	(13)	40	(15)	42	(13)	35	(17)	39	(12)	48	(17)	34	(16)	36	(5)
Peak flow rate (ml/sec)	20	(8)	17	(8)	24	(8)	15	(7)	25	(6)	18	(10)	30	(6)	14	(4)	17	(5)	12	(5)
Stress incontinence	100%		13%		100%		47%		100%		40%		100%		50%		100%		50%	

can see by examining the changes in peak flow rate and maximum voiding pressure in the 2 groups following surgery. In Group 1 the mean increase in maximum voiding pressure and the mean decrease in peak flow rate are probably significant (t-test), whereas in Group 2 the decrease in peak flow rate is significant but the mean maximum voiding pressure is virtually unaltered. From these results one can infer that on average the patients in Group 1 have had their urethras in some way "tightened" by the operation, whereas those in Group 2 may not have, and a change in bladder function may be partly responsible for the altered pressure studies postoperatively. This could be due to damage to the nerve supply to the bladder at operation, when the bladder is dissected medially off the vaginal fascia. One noticeable difference between the Group 1 and Group 2 patients is the number of previous operations for incontinence. The mean for Group 1 is 0.7 and for Group 2 is 1.2. There is no obvious reason for this discrepancy, as all the patients exhibited stable bladders prior to colposuspension.

The finding of detrusor instability following incontinence surgery has been previously documented. It has been noted following the implantation of an artificial sphincter (Hald *et al.*, 1975) and after a colposuspension (Worth, 1978). In neither of these cases has a cause been suggested. Many women date their symptoms of urgency and frequency of micturition back to a hysterectomy, although the incidence of detrusor instability is not increased following either abdominal or vaginal hysterectomy (Brown *et al.*, 1974). There are no adequate reports on pre-operative and post-operative urodynamic studies in patients undergoing other forms of pelvic surgery such as colporrhaphy.

We have divided the Group 2 (unstable) patients into types, as shown in our results. The numbers in these groups are too small for statistical evaluation. Group 2a is the most typical form of detrusor instability, exhibiting contractions greater than 15 cm of water. Four out of 5 of the patients in this group complain of urgency, urge incontinence and frequency of micturition. The Group 2b patients exhibit a rise of detrusor pressure only on posture change. Symptomatically and objectively they are more similar to Group 2a than Group 2c. This is borne out by the fact that 3 of these patients exhibited detrusor contractions when they returned for investigations one year later.

The Group 2c patients have an abnormally high detrusor pressure rise during filling. Although they complain of less urgency and frequency than the other 2 unstable groups, they have the highest incidence of stress incontinence post-operatively. We feel that these patients show "non-compliance" of the detrusor, and that it is a form of detrusor instability. Their bladders are not indistensible (Torrens *et al.*, 1975), as the mean post-operative capacity is not significantly lower than pre-operatively. In our experience the results of incontinence surgery were equally unsatisfactory in all 3 subgroups. This is contrary to the findings of Osborne (1978) who found, in a small series of patients with detrusor instability undergoing incontinence surgery, that almost all patients exhibiting detrusor contractions failed to be cured by incontinence surgery, whereas the success rate of the operation in the non-compliant patients was much higher, although they usually continued to complain of urgency and frequency. Another reason for classifying the non-compliant patients along with the other unstable ones is that at the later follow-up VCU one of them had altered to show an abnormal P2 rise and one of the patients at first exhibiting detrusor contractions has developed non-compliance.

We cannot speculate as to the reason for the variable manifestations of detrusor instability but it is interesting to note that although the type of instability may change, only one of the patients who underwent further VCU reverted to stability at a later date.

In view of the paucity of urodynamic data before and after other types of incontinence surgery it is impossible, at this stage, to incriminate the colposuspension as the only operative cause of detrusor instability. Our study does, however, underline the need for full urodynamic investigations in all patients in whom an incontinence procedure has failed.

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Vesicovaginal Fistulae

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Summary—The aetiology, methods of repair and results are described in 161 patients with vesicovaginal fistulae (26 also had rectovaginal fistulae). The cure rate was 81%.

Vesicovaginal fistula had been regarded as an incurable condition until Sims reported his successful work in 1852. There have been subsequent developments in techniques (Emmet, 1884; Mahfouz, 1938; Moir, 1964).

Patients and Methods

One hundred and twenty-eight patients were treated in Africa, mainly Ethiopia, and 33 in Britain, the age range being 16 to 68 years. The causes of the fistulae are shown in Table 1. Those due to malignancy, radiation or lymphogranuloma venereum have been excluded. The main obstetric cause was considered to be pressure necrosis of the bladder and/or rectum, associated with obstructed labour; in some patients operative delivery (forceps, caesarean section, caesarean hysterectomy) was also a factor. The typical history was of prolonged labour, often unattended, resulting in a stillbirth. Incontinence of urine and perhaps faeces followed, usually within a few days of delivery.

Fistulae following either obstetric or gynaecological surgery may be due to unrecognised or improperly repaired trauma, *e.g.* the inclusion of the bladder in a suture, or a haematoma followed by infection. "Other causes" included blind incisions in the vagina as part of local treatment for non-consummation, or even neglected foreign bodies in the vagina.

Twenty-six patients (one treated in Britain) also had rectovaginal fistulae. Twenty-nine patients had had previous attempts at repair (15 in Britain)—the number varying from 1 to 4 attempts.

Table 1 Main Cause of Fistulae

	Africa	*Britain*	*Total*
Obstetric	121	7	128
Pressure necrosis	121	3	
Caesarean section	0	2	
Caesarean hysterectomy	0	2	
Surgical	2	26	28
Abdominal hysterectomy	2	15	
Vaginal hysterectomy and/or repair	0	10	
Aldridge Sling	0	1	
Other	5	0	5
Total	128	33	161

The method of repair is shown in Table 2. A vaginal approach was adopted in 156 of the 161 patients, the lithotomy position being used in 142, the prone position in 14 patients. The details of the abdominal approach are not described in this report. It is not possible to describe a technique applicable to all fistulae but some important points are listed.

The waiting interval between injury and the attempt at repair is between 8 and 12 weeks. This allows for a reduction of oedema and infection; antibiotic therapy may be necessary. During the waiting period every effort should be made to make the patient as comfortable as possible, *e.g.* by the provision of incontinence pants and pads and the use of barrier or silicone cream for skin

Table 2 Operation

	Africa	*Britain*	*Total*
Approach			
Vaginal	126	30	156
Abdominal	2	3	5
Martius fat graft	126	9	135
Gracilis graft	12	0	12
Rectovaginal fistula also repaired	25	1	26

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protection. In Africa the patient often arrives in poor general condition, which responds to simple hygiene and nutritious diet provided in a waiting hostel with minimal nursing supervision.

In the pre-operative assessment and diagnosis the exact site of the fistula is ascertained and the possibility of more than one fistula involving the bladder or ureter or rectum should be considered. If stones are found in the bladder, these should be removed, the repair postponed, and therapy provided to eradicate infection and to avoid the development of further stones.

To achieve good exposure it may be necessary to perform a deep episiotomy at the outset. Any transverse fibrotic bands which are contributing to the vaginal stenosis should also be divided.

For both vesicovaginal and rectovaginal fistula repair, adequate tissue mobilisation is essential. All scar tissue must be divided and the bladder with its fistula freed. Scar tissue may be particularly dense anterolaterally, fixing the bladder to the pubis, or posteriorly to the cervix and uterus. The urethra may be totally destroyed as well as the bladder base. Repair in these cases requires reconstruction of the urethra. The ureters may be dangerously situated anywhere on the edge of the fistula and occasionally open on to the vagina. Ureteric catheterisation is then indicated. With the ureteric catheter in place, the dangers of suturing or injuring the ureter during the repair are avoided.

The fistula is repaired in 2 layers without tension with 2/0 atraumatic catgut or 3/0 atraumatic polyglycolic acid (interrupted inverting sutures). However, in many cases in Africa, because of fixation of the fistula to the pubic bone, an atraumatic needle is used to penetrate the periosteum (Hamlin and Nicholson, 1969).

A pedicle fat graft (Martius, 1939) from the labium majus provides additional support and vascularity in patients with a large fistula and with much scarring. Transplanting the gracilis muscle from its insertion into the tibia through a subcutaneous tunnel into the lower vagina will provide the necessary support in a small proportion of cases where the urethra and adjacent part of the bladder are totally destroyed (Hamlin and Nicholson, 1969). The gracilis muscle is divided at its cylindrical insertion, then freed up to its upper third where its blood and nerve supply enter. These must be carefully preserved. A tunnel is made deep to the skin and the superficial fascia of the upper thigh and labium, and the gracilis guided through. The lower half of the muscle is brought under the new urethra and repaired bladder fistula and firmly achored to the cervix, the lateral vaginal fascia, the fibrous connective tissue covering the periosteum on the medial borders of the ischiopubic rami and the periosteum on the lower anterior surface of the symphysis pubis.

The vaginal skin is closed with interrupted everting, non-absorbable sutures. Where there has been much vaginal stenosis and scarring there may be insufficient vaginal skin to effect closure and flaps of vulval skin can be swung in to help to close the defect.

Continuous free bladder drainage for 12 to 14 days post-operatively will give the repair time to heal. The type of catheter is less important than ensuring that there is never any blockage, *e.g.* by a blood clot, and that there is no "drag" on the catheter. The urinary output should be charted hourly so that any obstruction can be dealt with before the repair has been put to dangerous strain by bladder distension.

At a single operation for repair of vesicovaginal and rectovaginal fistulae it is usually easier for the rectum to be repaired first.

Follow-up for 3 weeks was all that was feasible in many of the African patients who travelled long distances. They were advised to return if incontinence recurred, and for delivery.

In Britain, follow-up was for at least one year.

Results

The details are shown in Table 3: 131 patients were cured at the first attempt. The 17 patients who had stress incontinence all had fistulae involving the urethra and bladder base. With perineal exercises over several months the stress incontinence disappeared in 7.

Thirty-three of the patients became pregnant within 1 year of the repair, 18 were delivered by caesarean section and 12 had vaginal deliveries—the outcome as regards the infant and the fistula repair was satisfactory. Three African patients delayed by poor communication had unattended

Table 3 Results

	Africa	*Britain*	*Total*	*Percentage*
Cure	100	31	131	81.4
Stress incontinence	15	2	17	10.5
Failure	13	0	13	8.1

deliveries which resulted in stillbirths and breakdown of the fistulae.

Discussion

The difference in the incidence and the type of fistulae seen in Africa and Britain is reflected in the availability of maternity services and the means of transport for the patients when labour is not progressing. In Britain, most cases are complications of pelvic surgery or the conditions which necessitated surgery. It is estimated that there are 250 post-hysterectomy vesicovaginal fistulae treated each year in Britain, according to the figures from the Newcastle Survey of 1969 to 1970 (J. B. Lawson, 1977; personal communication). Improvement in the maternity services should reduce the number of fistulae which are obstetric in origin. Such improvement may be difficult to achieve in some areas, especially where the population is largely rural and transport difficult, *e.g.* Ethiopia with its alternating mountains and deep gorges.

The repair of most genital fistulae, although exacting and time-consuming, is a very satisfying branch of surgery and success commonly follows for those who have been adequately trained in the techniques. Even so, in cases of much loss of tissue and scarring an expert may be taxed. Resort to urinary diversion is fortunately rarely required. In developing countries an abdominal stoma is often unacceptable as the maintenance of collecting bags and hygiene may be difficult. The selection of the operative approach (abdominal or vaginal) and the position of the patient (prone or lithotomy) will depend on the exact site of the fistula and the preference of the surgeon.

The use of the labial pedicle fat graft provides support and vascularity to the repaired fistula. The ability to have a subsequent normal delivery without breakdown of the repaired fistula may depend on the graft. Its supporting buttress action protects the repair during labour; it also helps to prevent stress incontinence.

The use of the gracilis is a modification of Ingelman-Sundberg's procedure (1954) for a higher bladder fistula and also provides additional blood supply and support in some cases. To prevent infection in this striated muscle, prophylactic antiobiotics are used.

Not all fistulae yield to a first operation. Each attempt at repair may result in more fibrosed tissue and stenosis, making subsequent surgery difficult.

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Complications of Antifibrinolysis Therapy after Prostatectomy

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Summary—As part of a trial to compare the effectiveness of various agents which have been claimed to reduce blood loss after prostatectomy, tranexamic acid (AMCA) was given pre-operatively and post-operatively to 6 patients having routine transurethral resections. Three of these developed indissoluble intravesical blood clots which persisted until they were evacuated surgically 5 to 17 days after cessation of AMCA therapy. AMCA cannot be recommended for routine use after prostatectomy.

Epsilonaminocaproic acid (EACA) has frequently been used after prostatectomy to reduce blood loss (Lawrence *et al.*, 1966; Madsen and Strauch, 1966; Vinnicombe and Shuttleworth, 1966). Tranexamic acid (AMCA) acts in the same way as EACA, but is 8 times more potent as an inhibitor of urokinase (Andersson *et al.*, 1968). AMCA has been recommended to control post-operative bleeding after prostatectomy (Hedlund, 1969; Kaufmann and Siefker, 1969). This recommendation has particular force since EACA, being unstable in solution, is no longer available in some countries. We report here a high incidence of persistent intravesical clots in patients given AMCA during and after prostatectomy.

Patients and Methods

As part of a trial designed to compare the effects of various agents which have been claimed to reduce blood loss after prostatectomy, 6 patients undergoing routine transurethral prostatectomy for benign prostatic hyperplasia were given AMCA, 1 g orally 6 h pre-operatively and 1 g tds post-operatively until macroscopic bleeding had ceased. The bladder was irrigated for 24 h post-operatively with 1 in 5000 chlorhexidine solution, through a 3-way Stewart catheter.

Results

Of the 6 patients treated with AMCA, 3 developed indissoluble blood clots in the bladder which were resistant to irrigation and persisted until they were evacuated surgically 5, 10 and 17 days after AMCA administration had been discontinued. The clots were firm, greyish in colour and adherent to the bladder wall. They caused discomfort to all 3 patients, delaying the discharge of 2 and causing a third to be readmitted with clot retention.

Discussion

EACA and AMCA are both antifibrinolytic agents which prevent the activation of plasminogen to plasmin in urine by the inhibition of urokinase (Andersson *et al.*, 1965, 1968). AMCA is much more potent than EACA. A single dose of 10 mg/kg produces antifibrinolytic activity in the serum for 8 h, and in the urine for up to 48 h (Andersson *et al.*, 1968). The reduction of fibrinolysis could run the risk of preventing destruction of blood clot, although it has been claimed that this has not been a problem with EACA (Madsen and Strauch, 1966; Vinnicombe and Shuttleworth, 1966). It is, however, interesting that 4 trials, 2 advocating the use of EACA (Lawrence *et al.*, 1966; Gordon-Smith *et al.*, 1972) and 2 of AMCA (Hedlund, 1969; Kaufmann and Siefker, 1969) after prostatectomy, each had a patient in the treated group with pulmonary embolism. In 3 cases the embolus was massive and fatal.

It has been shown that antifibrinolytic therapy in massive upper renal tract bleeding may produce problems with blood clot obstruction (Itterbeek

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et al., 1968), but previous authors advocating AMCA after prostatectomy (Hedlund, 1969; Kaufmann and Siefker, 1969) have not noted problems with persistent bladder clots.

Our experience indicates that blood clots occurring under the influence of potent inhibitors of fibrinolysis can be very persistent. Any advantage due to decreased post-operative blood loss was overshadowed, in the first 6 cases treated with AMCA in our trial, by the high incidence of complications, and the trial has been discontinued. AMCA cannot be recommended for routine use after prostatectomy.

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An Objective Look at Acid Phosphatase Determinations

A comparison of biochemical and immunological methods

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Summary—Measurements of serum and bone marrow acid phosphatase were made by 3 enzymatic methods, α-naphthyl phosphate, β-glycerol phosphate, and thymolphthalein monophosphate, and compared to a double antibody radioimmunoassay. Serum and bone marrow acid phosphatase levels were studied in 46 controls with histologically proven benign prostatic hyperplasia and in 135 patients with various stages of prostatic carcinoma.

In the control group the upper limit for bone marrow acid phosphatase was found to be significantly higher than the corresponding serum limit with respect to the enzymatic assays studied. The radioimmunoassay was the only method suitable for the analysis of the prostatic acid phosphatase content of bone marrow. A larger number of elevations were noted in patients with extracapsular and metastatic disease when prostatic acid phosphatase measurement was carried out by radioimmunoassay as compared to enzymatic methods. However, only 8% of the patients with intracapsular disease had elevations of prostatic acid phosphatase as measured by radioimmunoassay. Additional standardisation of immunological methods and clinical trials is required before comparison can be made of results from various centres using immunological methods for the measurement of prostatic acid phosphatase and a true assessment made of the usefulness of this procedure.

Accurate assessment of the extent of any neoplasm is necessary for its effective treatment. This is of particular significance in early disease when curative therapy is available. In carcinoma of the prostate the most effective method of assessing local spread is by removal of the gland and adjacent structures followed by careful histological examination of the complete specimen. Radical prostatectomy, however, has only limited indications in the treatment of this neoplasm and urologists must rely on more practical and less drastic procedures to assess the stage of the disease. Careful bimanual examination of the prostate gland with adequate biopsy specimens still provides the most accurate information with regard to the extent of local spread and histopathology.

Unfortunately, pelvic lymphangiography has proved to be an inaccurate method for assessing lymphatic spread in early disease, due to the inability of this technique to visualise adequately the primary drainage nodes and to demonstrate microscopic metastases (Bruce *et al.*, 1977). In patients suitable for radical surgery or radical radiotherapy, pelvic lymphadenectomy, on the other hand, provides more accurate information on the extent of metastatic nodal involvement (McLaughlin *et al.*, 1976; Bruce *et al.*, 1977).

Detection of blood borne extension of this neoplasm remains an unsolved clinical problem. Radiological methods (skeletal surveys and bone scans) lack the sensitivity necessary for the early detection of osseous metastases. Traditionally, elevations of serum acid phosphatase in patients with carcinoma of the prostate have been regarded as indicative of bone involvement. However, there has been much discrepancy between X-ray findings and elevations of serum acid phosphatase activity. London *et al.* (1954) have reported normal acid phosphatase levels in 40% of their patients with obvious skeletal metastases. Chua *et al.* (1970) and Gursel *et al.* (1974) have sug-

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gested that bone marrow acid phosphatase may be an early indicator of bone deposits, and Gursel *et al.* (1974) have shown the subsequent development of bone lesions in patients with carcinoma of the prostate in whom an elevated bone marrow acid phosphatase was the only early index of distant spread. Until recently, this enzyme has been measured in both serum and bone marrow by enzymatic methods and despite the use of different substrates and inibitors these assays have failed to detect, exclusively, acid phosphatase of prostatic origin (Kurtz and Valk, 1960; Boehme *et al.*, 1978). The application of immunological procedures, on the other hand, has brought about the recent development of potentially improved assays for the measurement of this tumour marker.

We wish to report the results of a study, in a series of controls and patients with different stages of carcinoma of the prostate, comparing 3 of the most acceptable enzymatic methods with a double antibody radioimmunoassay (RIA).

Patients and Methods

Blood samples (20 ml) were collected by venepuncture and bone marrow aspirates (10 ml) were withdrawn from either the posterior iliac crest or the sternum. The samples were allowed to clot at 4°C and following centrifugation the serum was separated from the clot and frozen at −20°C until analysis. After thawing the sample was divided into 2 portions, one for radioimmunoassay of prostatic acid phosphatase and the other for enzymatic study. Activity in the portion of the sample for biochemical analysis was stabilised, as described by Ewen and Spitzer (1976). The following substrates were utilised to measure acid phosphatase activity: α-naphthyl phosphate (Babson and Read, 1959), β-glycerol phosphate (Woodard, 1942) and thymolphthalein monophosphate (Ewen and Spitzer, 1976). The double antibody radioimmunoassay for the measurement of prostatic acid phosphatase in both serum and bone marrow was carried out as desribed by Mahan and Doctor (1978). This assay used as an antigen prostatic acid phosphatase purified from human ejaculate and shown to be identical to the enzyme purified from prostatic tissue. The data presented in Tables 1 to 4 were statistically evaluated using nonparametric methods of analysis, χ^2, as outlined by Snedecor and Cochran (1967).

Controls

Serum and bone marrow specimens were collected from 46 patients with histologically proven benign prostatic hyperplasia and analysed for prostatic acid phosphatase by RIA and enzymatic methods. The patients in this group ranged in age from 44 to 81 years with a mean age of 66.3 years.

Carcinoma

Prostatic acid phosphatase was analysed in the serum and/or bone marrow of 135 patients with various stages of prostatic carcinoma. A modification of the American urological system was used to stage these patients (Whitmore, 1956). The mean age of this group was 68.6 years with a range of 50 to 83 years. None of the patients included in this report was under any form of hormonal therapy at the time of study. The extent of the tumour localised to the prostate was assessed by careful bimanual examination under anaesthesia. Two biopsy specimens were taken from each lobe of the prostate for careful pathological study. Bone metastases were evaluated in every patient by technetium bone scans and, where indicated, bone tomography. In addition, lymphatic spread was assessed in 50% of the patients by block dissection of the pelvic lymph nodes at laparotomy.

Results

Table 1 shows the upper limits for serum and bone marrow acid phosphatase using all 4 methods. These levels were determined by establishing the 97.5 percentile in each category. The values for serum acid phosphatase in brackets represent the upper limits generally accepted for the respective assays. As shown, there was close correlation between our upper limits and estab-

Table 1 Upper Limits (Benign Prostatic Hyperplasia)

	Acid phosphatase	
	Serum	*Bone marrow*
α-Naphthyl phosphate	2.5 (2.5) i.u.	6.9 i.u.
β-Glycerol phosphate	0.9 (1.0) B.U.	2.4 B.U.
Thymolphthalein monophosphate	2.1 (2.0) i.u.	10.1 i.u.
RIA	7.6 (8.1) ng/ml	10.0 ng/ml

i.u.—International units.
B.U.—Bodansky units.
Numbers in parentheses indicate the accepted limits.

Table 2 Intracapsular Prostatic Carcinoma Percentage Elevations

	Acid phosphatase	
	Serum	*Bone marrow*
α-Naphthyl phosphate	12.2 (41)	6.5 (46)
β-Glycerol phosphate	4.5 (44)	0.0 (44)
Thymolphthalein monophosphate	2.3 (44)	2.0 (49)
RIA	8.3 (72)	3.3 (89)

Numbers in parentheses indicate the total number of patients.

lished values for all 3 enzymatic methods. In addition, the upper limit for the RIA in serum in this small group of controls compared very closely with a larger series of 411 controls (Mahan and Doctor, 1978).

On the other hand, the upper limit for bone marrow acid phosphatase was found to be higher than the corresponding serum level. This difference was most marked with the enzymatic methods. The bone marrow thymolphthalein level was 4.7 times higher than the serum value.

Intracapsular prostatic carcinoma (Table 2) represents A and B disease. In this group of patients approximately two-thirds were categorised as having B disease and one-third as having A disease. There was no statistical difference found in the elevations between the 2 groups of patients ($P=0.23$). All 4 methods showed a low percentage of elevations in serum (2.3 to 12.2%) and in bone marrow (0 to 6.5%).

More pronounced elevations were found in patients with extracapsular involvement (Table 3). A higher percentage of elevations was shown with the RIA in both serum and bone marrow samples as compared with the enzymatic methods. However, the prostatic acid phosphatase levels as measured by RIA were statistically higher only in bone marrow ($P=0.04$).

Table 3 Extracapsular Prostatic Carcinoma Percentage Elevations

	Acid phosphatase	
	Serum	*Bone marrow*
α-Naphthyl phosphate	26.6 (15)	6.7 (15)
β-Glycerol phosphate	12.5 (16)	6.3 (16)
Thymolphthalein monophosphate	12.5 (16)	6.3 (16)
RIA	35.2 (17)	20.0 (20)

Numbers in parentheses indicate total number of patients.

Table 4 Prostatic Carcinoma With Bone Metastases Percentage Elevations

	Acid phosphatase	
	Serum	*Bone marrow*
α-Naphthyl phosphate	81.8 (11)	54.5 (11)
β-Glycerol phosphate	66.6 (12)	66.6 (12)
Thymolphthalein monophosphate	70.0 (10)	50.0 (12)
RIA	95.2 (21)	96.2 (26)

Numbers in parentheses indicate total number of patients.

As shown in Table 4, the RIA was superior to the enzymatic methods for detecting prostatic acid phosphatase elevations in both serum and bone marrow in patients with obvious osseous metastases. Using enzymatic methods bone involvement was confirmed in 67 to 82% of patients when serum was analysed for acid phosphatase but in only 50 to 67% of patients when bone marrow was examined. On the other hand, approximately 95% of the samples in both groups were elevated when analysis was carried out by RIA.

Discussion

Although our control population was relatively small it was matched for age with the cancer group and limited to patients with histologically identified benign prostatic hyperplasia. In addition, all serum and bone marrow samples were studied using the 4 methods, and the upper limits were established separately for bone marrow and serum within the same group of patients. As shown in Table 1, the upper limits established for bone marrow acid phosphatase were higher than the corresponding serum values, regardless of the assay. This is a relevant observation because enzymatic studies continue to appear in the literature in which the upper limits of serum acid phosphatase are applied to the analysis of bone marrow acid phosphatase (Veenema *et al.*, 1977; Renoe, 1978). If such a concept was used in our study to examine bone marrow acid phosphatase levels then the sensitivity* of the enzymatic assays would be high for patients with proven bone

$$* \text{ Sensitivity} = \frac{\text{Diseased persons with positive test}}{\text{All diseased subjects tested}} \times 100$$

$$\text{Specificity} = \frac{\text{Non-diseased persons negative to test}}{\text{All non-diseased subjects tested}} \times 100$$

secondaries: α-naphthyl phosphate 92%, β-glycerol 83%, thymolphthalein monophosphate 92%. Unfortunately, the application of these lower serum limits would reduce drastically the specificity of the enzymatic methods. For example, only 32% of our control group would have normal levels of bone marrow acid phosphatase if the serum level for thymolphthalein monophosphate was applied to bone marrow. The corresponding values for α-naphthyl phosphate and β-glycerol phosphate would be 44% and 51% respectively. The high levels of acid phosphatase measured enzymatically in the bone marrow of our control group are apparently a result of the unavoidable lysis of normal cells during the process of bone marrow sampling. This releases a number of acid phosphatase isoenzymes into the bone marrow aspirate, which interfere with the enzymatic analysis of prostatic acid phosphatase. We have found that lysed platelets release an acid phosphatase isoenzyme which rapidly hydrolyses α-naphthyl phosphate and is inhibited by tartrate. However, when the same platelet supernatant was assayed for prostatic acid phosphatase by RIA no cross reactivity was observed (unpublished data).

By utilising the 97.5 percentile of the control group as the upper limit for bone marrow acid phosphatase the specificity of the assays was established. However, as shown in Table 4, the sensitivity of the enzymatic methods was then reduced by this analysis in our patients with bone involvement.

On the other hand, analysis of bone marrow acid phosphatase by RIA in patients with bone disease (Table 4) was statistically more sensitive than the corresponding enzymatic assays ($P=0.01$). Even with the more sensitive RIA, there was a variation of 2.4 ng/ml between the upper limits for serum and bone marrow in our control group. This might suggest the possibility of a degree of cross reactivity with antigens other than prostatic acid phosphatase in the analysis of bone marrow aspirates. However, no difference in the sensitivity of the RIA was noted when either the serum or bone marrow upper limits were compared in patients with bone disease. Thus immunological techniques offer a superior method for measuring the prostatic acid phosphatase content of bone marrow, and for assessing the potential role of this measurement in the diagnosis of early spread of carcinoma of the prostate. There appears to be little place for enzymatic methods in the study of this enzyme in bone marrow.

Chua *et al.* (1970) have suggested the existence of a blood-bone marrow barrier and/or a process of haemodilution to explain their success with bone marrow acid phosphatase as an earlier detector of metastatic disease. In the present study of patients with various stages of prostatic carcinoma, the percentage with serum elevations of prostatic acid phosphatase was higher than the percentage with bone marrow elevations. The only exception observed was in the analysis by RIA of patients with skeletal metastases. This would indicate no particular advantage in sampling bone marrow over serum for prostatic acid phosphatase. However, Drucker *et al.* (1978), using a radial immunodiffusion assay for prostatic acid phosphatase, have reported bone marrow values greater than serum values in 70% of patients with bone metastases. In contrast, using a double antibody RIA, for prostatic acid phosphatase we have found bone marrow elevations significantly higher than the corresponding serum values in only 5 of 21 patients with bony metastatic disease. The prognostic significance of this observation and the role of prostatic acid phosphatase analysis in bone marrow must await additional follow-up on our patients.

In the analysis of prostatic acid phosphatase in serum, no statistical difference was observed between the elevations found for α-naphthyl phosphate and the RIA procedure, although the percentage of elevations for RIA was considerably higher for patients with both extracapsular and metastatic bone disease ($P=0.2$). However, in the serum of patients with bone involvement a statistical difference was noted between the prostatic acid phosphatase values determined by RIA and β-glycerol phosphate ($P=0.04$) and also thymolphthalein monophosphate ($P=0.04$). It appears that α-naphthyl phosphate is the method of choice for those laboratories in which immunological methods are not yet available.

There is general agreement that immunological methods of analysis for prostatic acid phosphatase are superior to enzymatic procedures. However, marked discrepancies exist in the overall clinical results reported and in the interpretations made by the various investigators. Contrary to the report of Foti *et al.* (1977), the RIA procedure used in this study is not diagnostic of early prostatic carcinoma. Foti *et al.* (1977) have reported serum prostatic acid phosphatase elevations in up to 79% of patients with intracapsular disease using a solid phase RIA. In the present report, an elevation of 8.3% was noted for patients in this category using a double antibody assay. Chu *et al.* (1978) have reported elevations of prostatic acid phosphatase in 30% of patients with stage B disease using counter immunoelectrophoresis. Certainly a portion of the discrepancies noted could result in staging differences among the various centres. Therefore, before the role of immunological methods in the analysis of serum prostatic acid phosphatase can be accurately assessed, confirmation of reports is required. This will necessitate standardisation not only of immunological methods but also of the patient populations studied.

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Acid Phosphatase after Examination of the Prostate

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Summary—We report the effect of rectal examination of the prostate and transurethral resection of the prostate (TURP) on the serum level of tartrate labile acid phosphatase (TLAP) in 18 normal cases, 31 with benign enlargement of the prostate and 20 with carcinoma.

Rectal examination had no effect on TLAP in normal patients, those with benign enlargement and those with carcinoma, either after 5 min or the following morning. TURP for both benign and malignant disease raised the TLAP transiently with a rapid return to normal. We believe that there is no justification for postponing estimation of TLAP following rectal examination.

It has been suggested that acid phosphatase should be measured either before or more than 72 h after rectal examination of the prostate. This is based on the observation originally made by Hock and Tessier in 1949 that prostatic massage in patients with benign prostatic hypertrophy (BPH) caused an elevation of serum acid phosphatase to levels usually associated with prostatic carcinoma. Shuttleworth and Blandy (1976) pointed out that this belief is open to question. Yet in some urological centres (Murphy *et al.*, 1969) and clinical enzymology laboratories (Wilkinson, 1976), the "well-documented" rise in serum acid phosphatase, even after routine rectal examination alone, is accepted.

Until recently almost all of the determinations of serum acid phosphatase activity were made by various manual methods which gave results with poor reproducibility, especially in or near the low normal range of activity of this enzyme. Recently, automated methods of analysis have become available and Warren and Moss (1977) described an automated method for determining acid phosphatase activity with improved precision. We have used this method to re-examine the effects of prostatic examination on serum acid phosphatase activity in normal subjects and in patients with benign enlargement, with malignant disease of the prostate, or undergoing transurethral resection of the prostate.

Patients and Methods

All of the patients studied were in-patients with the exception of some with carcinoma of the prostate. They were divided into 3 groups:

Benign Enlargement. These patients had symptoms of outflow obstruction with or without acute retention, and glandular enlargement requiring surgical treatment. Histological confirmation of the diagnosis was made. Patients who had had previous surgery were excluded.

Malignant. These were new or known cases of prostatic cancer with histological confirmation, with or without extension beyond the gland.

Normal. These patients were admitted for non-prostatic operations and had no prostatic symptoms and a normal sized gland.

Routine rectal examination was performed on all patients. The size, consistency and contour of the gland were assessed and a search for rectal tumours was made. Prostatic massage was not carried out.

Blood samples were taken before and 5 min after rectal examination, then on the following morning (at least 12 h after), and the fourth morning after examination. Blood was withdrawn from antecubital veins with venous compression into airtight glass tubes, with no anticoagulants or other additives. Serum was separated within 2 h and stored deep frozen. Some samples were not separated immediately, but were stored at 4°C for periods of 6 to 18 h before being separated. After separation all serum samples were frozen immediately and kept frozen until immediately prior to analysis.

In some patients undergoing TURP, a similar series of samples was collected in relation to the operation.

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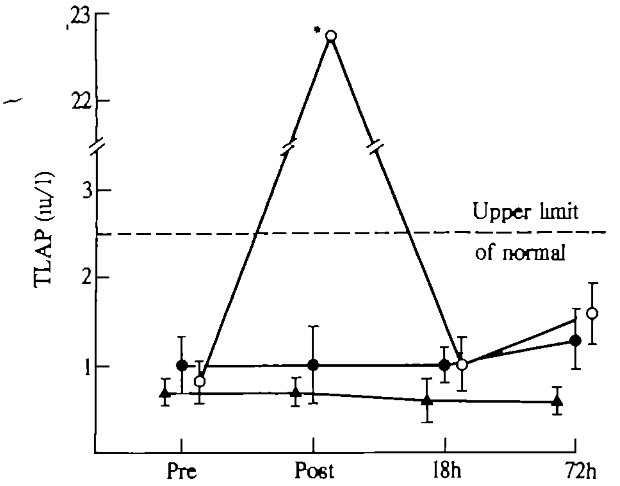

Fig. 1 Mean TLAP and standard deviation in normal patients (▲). Benign enlargement related to rectal examination (●) and benign enlargement related to TURP (○).
* SD=46.7. All values <25 except one of 176.3.

Samples were analysed at 37°C by the automated adaption of the Hillmann (1971) method for estimating serum acid phosphatase activity described by Warren and Moss (1977), with α-naphthyl phosphate as substrate. In this method, α-naphthol, released by acid phosphatase action, is coupled with a diazonium salt and the formation of this α-naphthyl-Fast Red TR azo compound is monitored continuously. Activities both with and without inhibition by L(+)-tartrate were measured. The upper limits of the reference range for this laboratory are: total acid phosphatase (TAP): 7.5 iu/l; tartrate labile acid phosphatase (TLAP): 2.5 iu/l.

Results

Rectal Examination

Sixty-seven patients were studied. Thirty-one had benign enlargement of the prostate, 20 had carcinoma and 18 were normal. There was no effect of rectal examination on tartrate labile acid phosphatase in any of these groups (Figs. 1 and 2). In only one non-malignant case was the post-examination level in the abnormal range. TLAP was also abnormal in the sample taken before examination. There was no instance in which rectal examination caused a rise into the abnormal range.

Table 1 Tartrate Labile Acid Phosphatase (iu/l) in Patients with Localised Carcinoma Who Had No Previous Treatment, in Relation to Rectal Examination

Stage	*Pre*	*Post*	*18 h*
2×0	0.6	0.8	0.9
2×0	1.1	2.0	
0×0	0.8	1.3	1.5
200	0.5	0.7	0.6
3×0	1.2	1.4	0.6

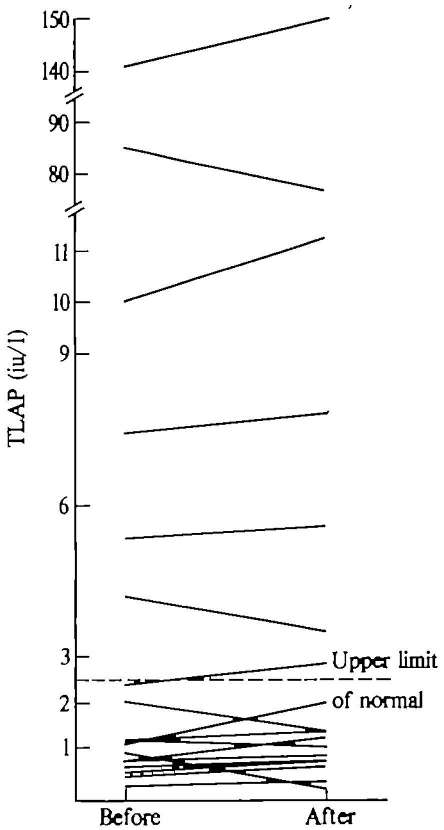

Fig. 2 TLAP before and after rectal examination in 19 patients with carcinoma of the prostate. Means before (13.3 iu/l) and after rectal examination (13.7 iu/l) showed no statistically significant difference. (Paired t-test: $P=0.38$.)

There were 5 patients in the malignant group who had had no previous treatment and no distant metastases (Table 1). In only 2 of these a small, insignificant rise occurred within the normal range.

Effect of TURP

Five patients with malignant disease were studied. Their details are shown in Table 2. There was no demonstrable effect on TLAP. Fourteen patients with benign enlargement were studied (Fig. 1). TURP produced a 100-fold rise in TLAP in one

Table 2 Effect of Transurethral Resection of the Prostate on Tartrate Labile Acid Phosphatase in 5 Cases of Prostatic Carcinoma

Tumour stage (TNM)	*TLAP (iu/litre)*			
	Before TURP	*After TURP*		
		5 min	*18 h*	*72 h*
3×0	7.4	7.8	6.1	missed
3×1	898	750	1050	450
210	1.5	lost	1.8	2.1
3×0	0.6	1.6	0.6	missed
4×1	136	162	123	204

case, but the increase was more usually 20-fold. In 5 cases, TLAP did not rise above 3.0 units. In all cases TLAP was normal the following morning.

Effect of Delay in Separation

The average values of samples (from normal patients and those with benign enlargement) which were separated immediately or some hours afterwards are shown in Table 3. There was a slight difference between the 2 groups, which can be accounted for by a greater number of normal specimens in the immediately separated group.

Discussion

It was shown in 1938 (Guttman and Guttman, 1938) that acid phosphatase could be detected in serum of patients with carcinoma of the prostate. In 1953 Fishman *et al.* developed a technique of assaying TLAP, which they showed to be the component of total serum acid phosphatase that was elevated in prostatic cancer. This led to the concept of "prostatic phosphatase" and the use of TLAP to investigate disease of the prostate. While it is true that in carcinoma of the prostate, TLAP is elevated almost exclusively, Dow and Whitaker (1970) have shown that normal levels of TLAP are present in the blood of normal men, normal women and men who have had cystoprostatectomy for bladder cancer. TLAP should not be referred to as "prostatic phosphatase" but is a good marker of carcinoma of the prostate.

Table 3 Tartrate Labile Acid Phosphatase Samples Separated Immediately or Some Hours Later, After Storage at 4°C

	Number	*Mean TLAP (iu/l)*	*SD*
Serum separated immediately	107	0.8	0.71
Serum separated later	40	1.1	0.42

Although the value of measuring TAP and TLAP in malignant prostatic disease is well-known, until recently the lack of precision and sensitivity have been important limitations of these assays.

The first obstacle, that of lack of reproducibility, both between and within laboratories has inevitably had clinical repercussions, with differing opinions on the usefulness of these assays and the effect or otherwise of various clinical procedures on these measurements. In utilising a kinetic approach, involving continuous monitoring of the reaction in an automatic enzyme analyser (Warren and Moss, 1977), we significantly reduced operator errors which occur when carefully timed manual methods are used in large scale routine practice. Furthermore, we have excluded the possibility of non-linear progress curves, which have to be assumed in 2-point manual assays.

Secondly, in this method, use was made of α-naphthyl phosphate, one of the more selective substrates for prostatic acid phosphatase (Babson *et al.*, 1959; Roy *et al.*, 1971; Shaw *et al.*, 1977) as opposed to acid phosphatases from red blood cells, bone and other tissues. The measured TAP is made even more specific at elevated levels by assaying the tartrate inhibited fraction (Jacobsson and Landberg, 1964).

The reproducibility of our results (Table 4), when compared to a standard manual method, marks a step forward in tackling one of the limitations of these assays.

Effect of Rectal Examination

Raised serum acid phosphatase after prostatic massage was first reported nearly 20 years ago, using the then available manual methods. We have taken advantage of recent improvements in precision in analytical techniques and used, for the first time, these methods to reassess TAP and TLAP after prostatic examination.

There have been reports both confirming and failing to confirm Hock and Tessier's observation in 1949 of a raised level of acid phosphatase following massage in 17 of 20 patients with a variety of prostatic diseases. In fact, only 4 of these increments reached abnormal levels. Other reports

Table 4 Comparison of Precision of Measurements of Acid Phosphatase Activity at 37°C by our Method and a Standard Manual Method (King and Jegatheesan, 1959) in a Clinical Setting (n is the Number of Replicate Estimations)

	Total activity (iu/l)			*Tartrate-labile activity (iu/l)*		
	Mean	*SD*	*Coefficient of variation (%)*	*Mean*	*SD*	*Coefficient of variation (%)*
A. LKB 8600 Kinetic α-naphthyl phosphate method						
Between batch	9.7	±0.6	±6.5 (n=51)	8.95	±0.69	7.75 (n=51)
B. Standard 2 point phenyl phosphate manual method						
Between batch	15.4	±2.7	±17.5 (n=21)	13.8	±1.4	10.2 (n=21)
				0.5	±0.2	±40 (n=30)

(Bonner *et al.*, 1954; Roubicek and Winston, 1962) of increase in most or all patients with benign enlargement considered only small numbers, although 50% of Bonner's patients reached the abnormal range. Their patients received a thorough prostatic massage (3-5 min). Others have reported a much smaller incidence of abnormal values of TLAP following vigorous prostatic massage: Kendall (1961) reported changes in 5 of 75 patients; Fishman *et al.* (1956) reported a rise in 7 of 123 patients, but only 4 reached the abnormal range, contradicting Bonner's earlier findings. Owen and Van Zyl (1952) noted abnormal levels in 3 of 24 patients following routine rectal examination. Other investigators have been unable to demonstrate a rise to abnormal levels following massage (Dybkaer and Jensen, 1958; Finkle *et al.*, 1961) or routine rectal examination (Marshall and Amador, 1969; Christensen and Nielsen, 1972). Most of these authors show that TLAP varies within the normal range following massage.

These results are not entirely comparable with our study. Firstly, the degree of prostatic manipulation varied from 5 min massage to routine rectal examination lasting less than 30 sec. Secondly, blood samples were taken at various intervals after massage. Usually the highest recorded level was at one hour or less, but often the earliest sample was at half or one hour. If the enzyme is released from the gland at the time of palpation, the peak level will be reached much sooner than this, as soon as the enzyme is distributed in the total blood volume. We have confirmed here the rapid elimination of the enzyme from the blood which has been observed by others (Dybkaer and Jensen, 1958; Finkle *et al.*, 1961) and is expected from the knowledge that TLAP is unstable at 37°C in blood at physiological pH, so an early sample is necessary to detect a rise attributable to the manipulation. Thirdly, the assay of TLAP was done by various manual methods which were open to operator error, to variation between methods and to variability within the methods.

We have sought to avoid these errors and to place the observations in a clinical setting. The prostate was examined as part of routine clinical examination. No attempt at massage was made. The blood samples were taken at a time (5 min after examination) when the level of enzyme was expected to be highest, which is also a convenient and customary time for taking blood, at the end of the clinical examination. In view of the various recommendations that blood sampling must be delayed 24 to 72 h, we measured TLAP the following morning and after 3 full days. The measurements were made on an automatic analyser, which made the results more reliable, as we have shown.

In neither patients nor controls was there any elevation of TLAP following rectal examination. Thus several earlier reports have been confirmed, using an objective assay method in a clinical setting. There is no basis for the custom of delaying blood sampling for acid phosphatase following rectal examination.

In one case of benign enlargement with acute retention, TLAP was elevated both before and after rectal examination but was normal the following day. The practice of taking blood before rectal examination would have been no safeguard in this case.

Previous workers have shown as much disagreement over increments in TLAP after prostatic examination in patients with cancer as in patients with benign enlargement. Some say that a rise is indicative of *in situ* carcinoma (Fishman *et al.*, 1956), others that a rise is to be expected only if TLAP is already elevated (Bonner *et al.*, 1954; Roubicek and Winston, 1962). In our patients with carcinoma, no rise was detected following rectal examination. This fails to support the proposal (Fishman *et al.*, 1956; Kendall, 1961) that a rise following rectal examination is suggestive of early carcinoma.

Effect of TURP

The measurements of TLAP in relation to TURP are of interest. They show an expected immediate rise of TLAP. Even when this rise is 150-fold, the following day the level is normal. This demonstrates the rapid elimination of TLAP from the circulation and amply confirms that the much smaller amounts of enzyme that might be released by rectal manipulation would be insufficient to maintain abnormally high blood levels.

The wide variation in TLAP following TURP is probably related to the amount of prostatic tissue destroyed and the degree of vascular damage produced. The lack of any effect of TURP on TLAP in carcinoma is probably related to both the more limited resection usually performed in this disease, and the fact that cancerous tissue contains less acid phosphatase than normal or hyperplastic glands (Woodard, 1959).

Effect of Delay in Separation

The lack of any significant difference in the TLAP average values between those samples separated immediately and those processed after some hours' storage at 4°C is largely due to the relative insensitivity of our substrate (α-naphthyl phosphate) to erythrocyte acid phosphatase. In addition, our routine use of TLAP further reduces the inclusion of other non-prostatic acid phosphatases in the serum.

Doe and Seal (1965) reported a diurnal variation in serum TLAP related to adrenal steroid production. In our study, samples were taken in relation to rectal examination at various times of day, whereas subsequent samples were usually taken in the morning. No difference is observed, so this effect can be ignored.

Our TAP and TLAP methods do not resolve the other major limitation of these assays in clinical practice mentioned earlier, *viz.* the lack of sensitivity for measuring the very small differences in amounts of circulating serum acid phosphatase. The recent application of solid-phase radioimmunoassay to the measurement of specific serum prostatic acid phosphatase (Foti *et al.*, 1977) demands serious attention as a possible answer to this problem of sensitivity.

Despite being at the limits of sensitivity for our method, we observed a small but consistent difference in TLAP levels between normal subjects and patients with BPH, which may be related to the different amounts of prostatic tissue present. We found the expected higher TLAP levels in those patients with carcinoma of the prostate.

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The Early Results of Treatment of Stricture of the Male Urethra Using the Sachse Optical Urethrotome

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Summary—Thirty-nine male patients with urethral stricture have undergone urethrotomy using the Sachse optical urethrotome. Post-operatively a urethral catheter was used for 24 to 72 h. The technique is simple, the stay in hospital is short and complications are uncommon.

Eighty-two per cent of the patients are now symptom-free and a further 13% are sufficiently improved to be able to void satisfactorily at follow-up varying from 4 months to 2½ years (mean 12 months). The 2 patients in whom unsatisfactory results were obtained had long strictures.

We feel that direct vision urethrotomy should be considered as a treatment for urethral stricture.

The management of urethral stricture in the male is one of the oldest problems known to urology. The most common method of treatment is probably regular urethral dilatation. This method had disadvantages in that patients have to be treated at intervals over many years, often by a wide variety of clinicians with variable expertise. Urethral trauma and false passages may occur and there is the risk of urinary infection and bacteriaemia.

Urethroplasty using skin flaps (Blandy, 1975) seemed to offer better prospects for patients with stricture but the technique may be a major procedure for an elderly patient, especially if it has to be performed in 2 stages. Our initial enthusiasm for urethroplasty has been dampened by the post-operative complications of diverticulum formation, hair stones and recurrent strictures.

Urethrotomy is an ancient technique which attained great popularity in the eighteenth and nineteenth centuries. Being a blind procedure, however, it could often result in severe bleeding or acute discomfort to the patient. Nonetheless, excellent results with urethrotomy have been reported by Helmstein (1964), who advocated the use of urethroscopy before and after blind urethrotomy to enable the stricture to be accurately localised and checked for a satisfactory incision. More recently, as a result of technical advances in instrument design, it has been possible to carry out urethrotomy under direct vision using an optical urethrotome. Initially, incision of the stricture was performed using an electro-cautery technique (Ravasini, 1957), but in the last few years incision by means of a scalpel has been developed (Sachse, 1974).

We have been using the Sachse optical urethrotome in the management of urethral strictures and would like to present the encouraging early results.

Patients and Methods

Thirty-nine patients with urethral stricture have been treated by Sachse urethrotomy over the past 2 years. Their ages ranged from 5 to 90 years (mean 59.4 years). The aetiology of the strictures is shown in Table 1. The duration of symptoms ranged from less than 1 year in 19 patients to over 10 years in 3. The site and length of the

Table 1 Aetiology of Stricture

Traumatic	6
Infective	7
Post-operative	
Urethroplasty	1
Retropubic prostatectomy	5
Transvesical prostatectomy	4
Transurethral prostatectomy	9
Unknown	7
Total	39

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Table 2 Site of Stricture

Anterior urethra	3
Bulb of urethra	13
Membranous urethra	12
Bladder neck	11
Total	39

Table 3 Length of Stricture

Diaphragm	9
0-½ cm	14
½-1 cm	11
1 cm +	5
Total	39

strictures are shown in Tables 2 and 3. The patients in the early part of this series had undergone regular dilatation but in 19 of the later patients Sachse urethrotomy was the primary treatment.

The instrument (as supplied by Storz Ltd) consists of a panendoscope sheath with a 0° or 30° viewing lens. The scalpel is similar to that used in neurosurgery and consists of an anterior and superior cutting edge (Fig. 1). It is mounted on 2 carrying rods and inserts into a Nesbit action electrotome. The instrument is inserted into the urethra and the stricture visualised (Fig. 2). Through its side arm a small ureteric catheter may be passed across the stricture in order to show the line of the urethra beyond. The stricture is then cut by using an upward movement of the blade (Figs. 3a, b, c and d). The whole instrument is used and cutting is continued until all of the fibres of the stricture have been divided. It is quite easy to identify these fibres and when cut they can be seen to spring apart quite readily. Very often the incision has to be carried into the wall of the urethra and bleeding may be encountered. When this happens, the ureteric catheter can be withdrawn and a simple electrode passed to cauterise the bleeding points. After full incision of the stricture has been performed the rest of the urethra, the bladder neck and the bladder can be inspected. The instrument is available in a paediatric size if required.

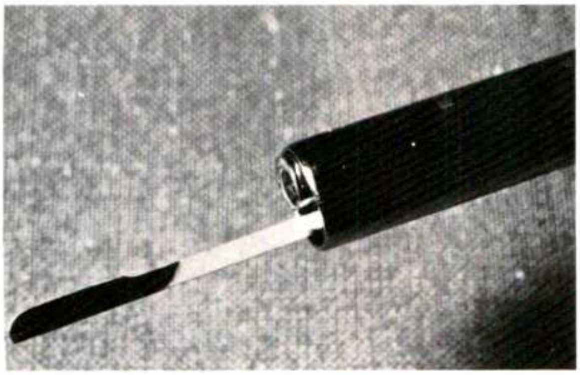

Fig. 1 Sachse urethrotomy blade projecting through panendoscope sheath, showing anterior and superior cutting surface.

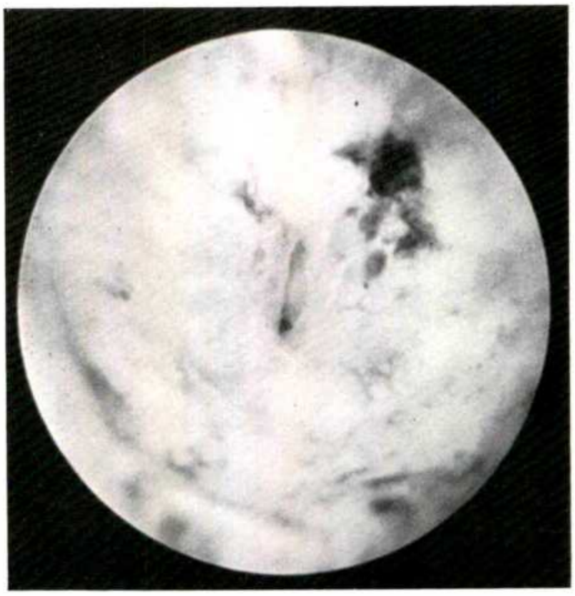

Fig. 2 Panendoscope view of post-prostatectomy urethral stricture.

Following incision of the stricture a fenestrated catheter is left in place for a period varying from 24 to 72 h. Sachse (1974) suggested that catheters should be left longer to hold the edges of the incised urethra apart, but this does not appear to be necessary.

Results

Thirty-nine patients with urethral stricture have been treated using a Sachse optical urethrotome. The duration of follow-up varies from 4 months to 2½ years (mean 12 months). Thirty-two patients are symptom-free, 5 patients have improved enough for further treatment to be unnecessary, and in 2 patients there has been no sustained improvement. In 4 patients a second urethrotomy has been necessary.

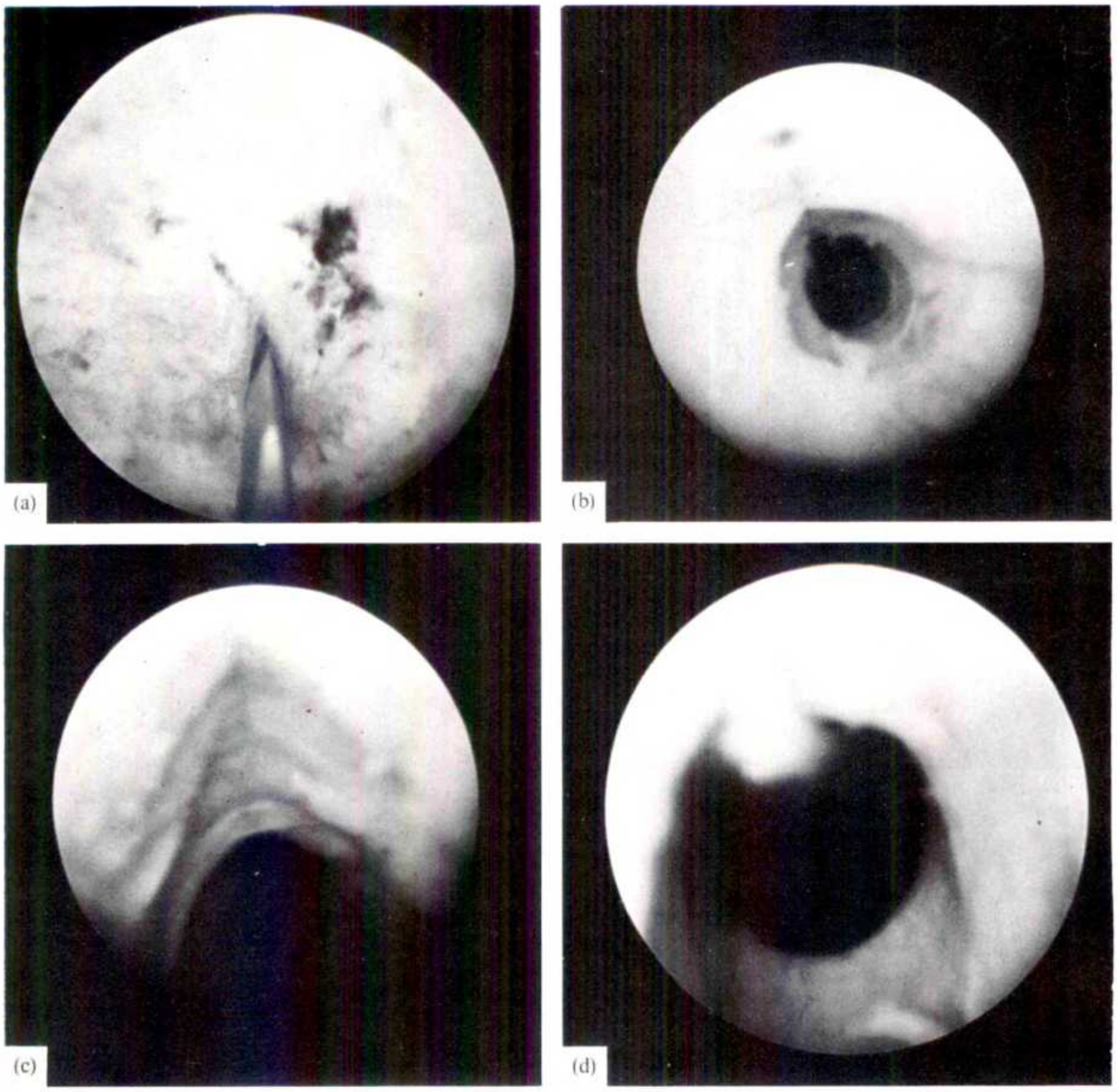

Fig. 3 (a) Sachse blade inserted into stricture (ureteric catheter not used on this occasion). (b) Initial division. (c) Further division of layers of stricture. (d) Complete division of stricture fibres allowing panendoscope to pass easily into the bladder. Bladder neck visible in the distance.

In the 2 patients with no symptomatic improvement the strictures formed again in less than 4 weeks. One patient had a 3 to 4 cm stricture in the bulb which closed down rapidly after each of his 3 urethrotomies. In the second patient, who had a 1 cm stricture in the bulb, symptoms recurred within 4 weeks of urethrotomy. In the group of 5 improved patients, 2 had urethrotomy for post-prostatectomy bladder neck strictures and have adequate urinary streams 2 years and 8 months later respectively. Two patients with strictures in the bulb had been well for 5 and 7 months respectively before symptoms returned. Finally, one patient had urethrotomy for a 1 cm stricture of the membranous urethra which had been dilated regularly at 8-week intervals for 20 years; he was symptom-free for one year before a diminution in his urinary stream recurred.

Complications in this series have been few. One patient had severe post-operative bleeding and required a blood transfusion; one patient developed a secondary haemorrhage and had to be re-admitted for transfusion. Two patients developed post-operative pyrexia with urinary infection which quickly settled on the appropriate antibiotic. One patient with a long anterior stricture developed extravasation of the irrigating fluid during the urethrotomy. The procedure was abandoned but after 2 days of catheter drainage the tissues had returned to normal and the urethrotomy was completed with a satisfactory result.

All patients were followed up as out-patients and assessed primarily by symptoms; patients with strictures can very accurately assess the effectiveness of treatment by their urinary flow. Some patients had urethrography and flow rate studies, but these investigations were not performed on a sufficient number to warrant discussion. Such results as are available support the findings of Lipsky and Hubmer (1977), who showed a close correlation between symptomatology and flow rates.

Discussion

Regular dilatation is an established and well recognised treatment for stricture of the male urethra. Urethroplasty offers a permanent cure and good results have been reported (Schmeidt, 1973; Blandy *et al.*, 1976). However, these procedures have their disadvantages and our experience suggests that urethrotomy under direct vision should now be considered as an alternative.

The technique allows inspection of the whole stricture and complete division of all scar tissue under vision. The straight incision of the scar appears to inhibit restenosis and our results confirm those of Sachse (1974) and Lipsky and Hubmer (1977), that urethrotomy using an optical urethrotome produces complete and, in the majority of patients, sustained relief of symptoms.

Urethrotomy is most effective when the stricture is short (3 cm or less) and in the region of the membranous urethra. It is also effective in the treatment of strictures of the bladder neck. On the other hand, strictures in the anterior urethra are difficult to incise because of the problems involved in manoeuvring the instrument in this mobile area. In one patient, extravasation of the irrigating fluid occurred into the penis and scrotum. However, this fluid, isotonic saline, was rapidly reabsorbed. The bleeding that occurred post-operatively in one patient early in the series was probably due to carrying the incision too deeply into the urethral wall. With experience, this complication has been avoided in subsequent cases.

In 2 patients skip strictures were encountered. The value of this instrument in the onward visualisation of the urethra following division of the stricture is emphasised, for in each case further concomitant urethrotomy in the proximal urethra easily disposed of the second stricture. In one patient a secondary bladder neck obstruction was detected and urinary symptoms remaining after urethrotomy were eliminated by a subsequent transurethral resection.

It would seem that, by completely dividing the circumferential fibres of a stricture, not only is immediate relief obtained but any subsequent contracture of the scar tissue will, if anything, tend to open the urethra further. However, urethrotomy can be repeated easily, without risk to the patient, should the stricture be incompletely incised or should restenosis occur. Regular dilatation or urethroplasty can be substituted without difficulty if urethrotomy fails.

Sachse (1974) suggested that in the post-operative period a urethral catheter should be left for 10 to 14 days in order to hold the edges of the incised urethra apart. Lipsky and Hubmer (1977) removed the catheter after 7 days. We have left our catheters for only 24 to 72 h in order to reduce the risk of infection and encourage early discharge of the patients. Our results compare favourably with those of Sachse (1974) and Lipsky and Hubmer (1977) and we feel that the prolonged period of catheter drainage which they describe is not justified.

Acknowledgements

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Balanitis Xerotica Obliterans

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Summary—Twenty patients with histologically proven balanitis xerotica obliterans have undergone different forms of treatment; their progress has been reviewed and discussed.

Balanitis xerotica obliterans involving only the foreskin was best treated by circumcision. The patients in whom meatal stenosis was present responded well to regular meatal dilatation, meatotomy followed by regular dilatation and, in advanced cases, to meatoplasty.

At present there is no evidence to indicate that associated urethral strictures, proximal to the fossa navicularis, are due to balanitis xerotica obliterans.

Balanitis xerotica obliterans (BXO) is a well-defined condition, with specific clinical and histological features, whose aetiology is still unknown. The disease has been defined as a local manifestation of lichen sclerosus et atrophicus (Laymon and Freeman, 1944) involving the prepuce, glans and coronal sulcus, with or without involvement of the fossa navicularis. Involvement of the urethra is limited to the external meatus and squamous epithelium of the fossa navicularis (Bainbridge *et al.*, 1971).

BXO is an uncommon disorder and clinicians may be undecided as to the best form of treatment. Some authors have recommended topical and sublesional corticosteroids for meatal stricture (Catterall and Oates, 1962; Poynter and Levy, 1967), while others have advised meatoplasty (Blandy and Tressider, 1967; Bainbridge *et al.*, 1971). This study was carried out in order to determine the best method of treatment.

Patients and Methods

A review was carried out on 20 patients with histological proof of BXO who attended the Departments of Surgery and Urology at the Bristol United Hospitals between 1969 and 1978.

The age at presentation varied between 13 and 85 years, with a mean of 46 years. The main presenting symptoms were difficulty with micturition, non-retractable foreskin, pain and difficulty during intercourse and urinary retention (Table 1). The length of history ranged from 4 months to 13 years with a mean of 2½ years. Eighteen of the 20 patients were married, 4 had evidence of previous urinary infection and 2 had a past history of venereal disease. Three patients had previously undergone circumcision and one had had partial amputation of the penis 3½ years before presentation.

This review covers a considerable period of time and it is not surprising that the patients were seen by different surgical teams and subjected to different forms of treatment (Table 2).

Results

The overall results of treatment were encouraging. Thirteen patients (65%) became symptom-free, 5 (25%) showed satisfactory improvement, one patient showed some improvement in symptoms and in the last patient the results were difficult to assess.

Table 1 Presenting Symptoms

	No. of patients
Difficulty with micturition	6
Non-rectractable foreskin and difficulty with micturition	4
Non-rectractable foreskin, swelling, difficulty with micturition and cystitis	3
Non-retractable foreskin, swelling, pain and difficulty during intercourse	3
Urinary retention	3
Haematuria	1
Total	20

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Table 2 Methods of Treatment

	No. of patients
Circumcision alone	8
Circumcision and meatal dilatation	3
Circumcision and meatotomy	2
Circumcision and meatotomy followed by 2-stage urethroplasty	1
Circumcision and meatotomy followed by meatal dilatation and application of steroid cream	1
Circumcision and meatotomy followed by meatoplasty	1
Meatotomy alone	1
Meatotomy followed by meatoplasty	2
Meatotomy followed by meatal dilatation	1

The results have been analysed in relation to the clinical findings and divided into 4 groups:

(1) Five patients with BXO limited to the prepuce were treated by circumcision. There has been no recurrence and they have remained symptom-free for 2 to 9 years.

(2) Three patients with meatal stenosis were treated by meatotomy. One patient responded well and has been symptom-free for 2 years, but in the other 2 cases the treatment was unsuccessful. Both patients subsequently underwent meatoplasty and have remained symptom-free for 2 and 5 years respectively.

(3) The results of treatment in 6 patients with BXO involving the foreskin and meatus, or the foreskin, glans and meatus, are subdivided as follows: One patient treated by circumcision and meatotomy has improved symptomatically but 3 years later still has some difficulty with micturition. Three patients who underwent circumcision and meatal dilatation have shown satisfactory improvement. One patient treated by circumcision and meatotomy, followed by dilatation and application of a topical steroid cream, has been symptom-free for 4 years. The last patient in this group was treated within the last year by circumcision and meatotomy, followed by a first-stage urethroplasty, and it is too early to assess the result.

(4) Six patients had involvement of the meatus and glans, the meatus and frenulum or the glans and foreskin. Three of these patients had no meatal involvement and following circumcision 2 have remained symptom-free for 7 and 9 years respectively, whilst the third has maintained satisfactory improvement for 9 years. The remaining 3 patients with meatal involvement have each been treated differently. One had circumcision and meatotomy and has shown symptomatic improvement for 6 years; 1 had circumcision and meatotomy followed by meatoplasty and has been symptom-free for 4 years; the third had meatotomy followed by meatal dilatation and has been symptom-free for 8 years.

Discussion

BXO may occur following circumcision (Stuhmer, 1928) or after a preputial tear (Madden, 1935), but more recent studies have failed to establish circumcision as a causative factor (Laymon, 1951; Catterall and Oates, 1962). Only 3 patients in this series had undergone circumcision before presenting with BXO and this is at variance with Stuhmer's findings in 1928.

The 5 patients with involvement of the foreskin only have remained symptom-free following circumcision and this supports the recommendation by Bainbridge *et al.* (1971). In this series the results of treatment by meatotomy, meatal dilatation, and meatoplasty with or without circumcision for meatal stenosis, compare favourably with other published results. Catterall and Oates (1962) used hydrocortisone acetate injections for treatment of meatal stenosis and reported a cure rate of only 24% and an improvement rate of 29% in 21 patients.

One patient with histological proof of BXO involving the foreskin and meatus was treated by circumcision and meatal dilatation, followed by an anterior 2-stage urethroplasty for stricture, but none of the histological sections revealed BXO involvement of the urethral stricture (Bainbridge *et al.*, 1971). In the cases of urethral involvement in BXO reported by Staff (1970) no precise histological evidence was given and it would seem equally probable that these strictures were due to previous instrumentation or inflammation. At present there is no evidence to indicate that associated strictures of the urethra are also due to BXO.

Three patients with meatal stenosis who failed to respond to meatal dilatation or simple meatotomy have become symptom-free following meatoplasty. This supports the view of Blandy and Tressider (1967) that meatoplasty is an effective form of treatment for meatal stenosis.

It is concluded that BXO involving the foreskin is cured by circumcision. The patients in whom meatal stenosis is present respond well to regular meatal dilatation, simple meatotomy followed by regular dilatation and, in advanced cases, to meatoplasty. Involvement of the foreskin and meatus, or the foreskin, meatus and glans, is best treated by a combination of circumcision and meatal dilatation, meatotomy or meatoplasty.

In this review there was no evidence to indicate that associated strictures of the urethra were also due to BXO.

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British Journal of Urology (1979), **51**, 232

Case Reports

Polycystic and Horseshoe Kidneys in the Same Family

We wish to report a family with adult polycystic renal disease in whom there are 3 offspring of affected individuals who have a horseshoe kidney. The latter 3 patients were investigated when aged 17, 19 and 22 years and there was no radiological evidence of polycystic disease affecting the horseshoe kidneys.

The family tree appears in the figure.

Discussion

Adult polycystic kidneys are inherited as an autosomal dominant with the dominant gene having a very high penetrancy. Many of these patients also have other anomalies such as hepatic and pancreatic cysts and cerebral aneurysms. This suggests that a single gene may have multiple effects and possibly be modified by certain environmental factors.

Boatman and Hawtrey (1973) were possibly the first to recognise the familial occurrence of horseshoe kidneys when they reported 2 affected sisters, while David (1974) presented details of a family having 3 siblings with horseshoe kidneys and their mother who had a rotational abnormality of 1 kidney. Horseshoe kidneys result from an embryonic fault between the fourth and eighth week of foetal life where there is fusion of the renal blastemas when the primitive kidneys are in close proximity and still anteriorly related. One-third of patients with horseshoe kidneys have been found to have associated congenital malformations, a proportion of which involve the urogenital tract. There have been isolated reports of polycystic horseshoe kidneys (Correa and Paton, 1976).

We are unaware of any family with polycystic renal disease where affected family members have produced offspring with horseshoe kidneys.

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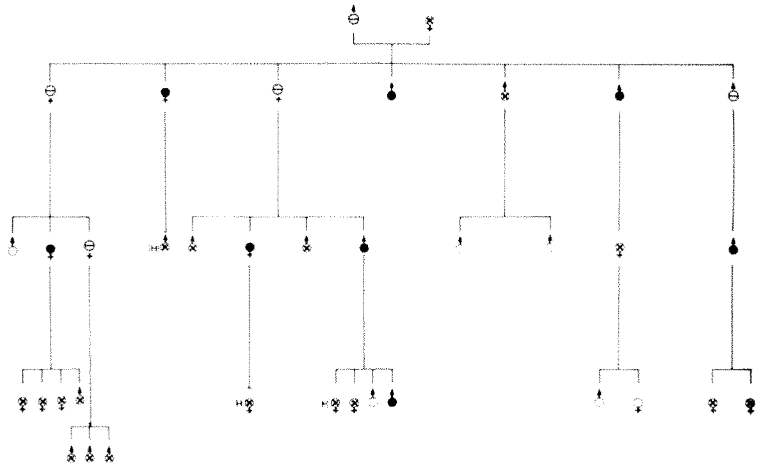

Fig. Family tree. Key: ● proven polycystic renal disease; ⊖ died of renal failure—probably polycystic; ⊗ not polycystic; ○ not investigated; H horseshoe kidney.

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Fibrous Polyp of the Ureter

Fibrous polyps of the ureter are benign tumours of mesodermal origin. They are very uncommon and a recent review of the literature showed 37 cases (Stuppler and Kandzari, 1975).

Case Report

A 24-year-old man was admitted to the hospital with a several-month history of intermittent crampy abdominal pain on the right side. Physical examination was unremarkable except for a left varicocele. Urinalysis showed many red cells. Intravenous urography revealed an elongated smooth filling defect in the lower third of the right ureter above a small radio-opaque stone (Fig. 1).

The patient underwent exploration of the right lower ureter. The stone was removed through a longitudinal ureterotomy and a glistening worm-like polyp extruded, measuring 3 cm in length, attached by a narrow stalk to a small area of the ureteric wall. A 3 cm ureteric segment was excised with the lesion and an end-to-end anastomosis was carried out. Convalescence was uneventful and follow-up IVP was normal.

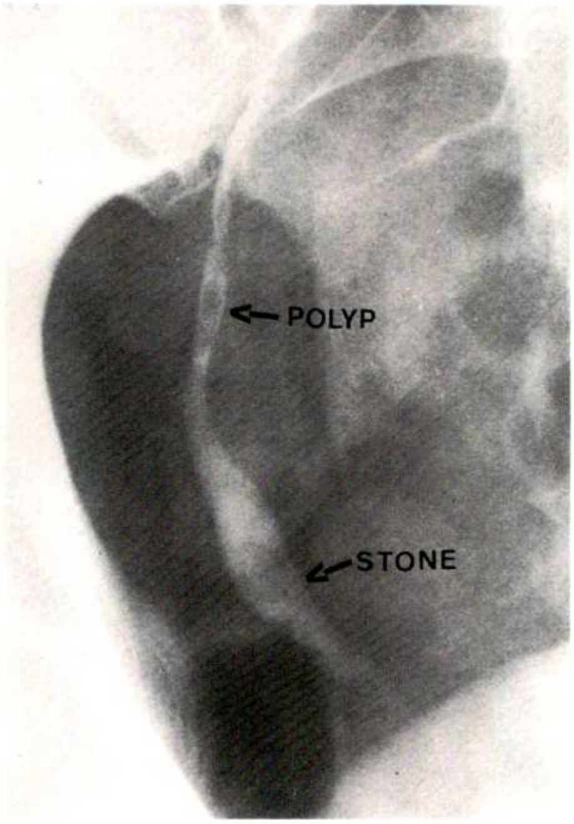

Fig. 1

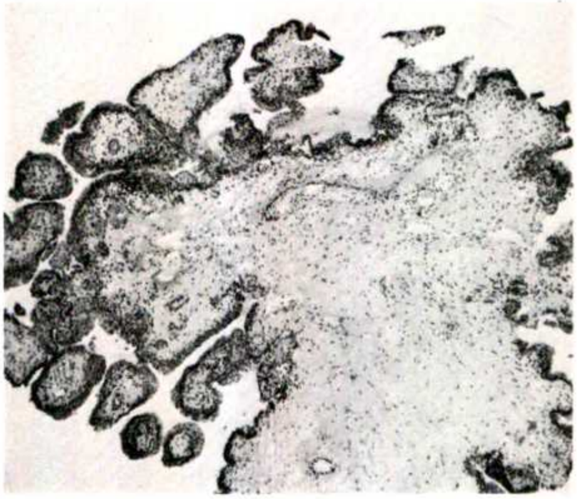

Fig. 2

Microscopic examination revealed fibrous stroma lined by normal transitional cell epithelium (Fig. 2). The pathological diagnosis was fibrous polyp of the ureter.

Comment

Fibrous polyps of the ureter have been reported in patients of all ages of life. Their most common location is the ureteropelvic junction or the upper ureter. The aetiology of this tumour is not well established. Fibrous polyps are frequently associated with urinary infection or chronic irritation of the ureteric wall, as in our patient, carrier of a ureteric stone for several months. However, the absence of infection in many cases and the youthful age of some patients suggest also a congenital origin. The characteristic radiological finding is a smooth and often elongated intraluminal filling defect. Local excision of the polyp with partial ureterectomy or simple fulguration is the treatment of choice.

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Stuppler, S. A. and Kandzari, S. J. (1975). Fibroepithelial polyps of ureter. *Urology*, **5**, 553-558.

The Author

M. Vandendris, Department of Urology, Brugmann University Hospital, Brussels, Belgium.

British Journal of Urology (1979), **51**, 234

Primary Vaginal Stone following Abdomino-perineal Excision of the Rectum with Total Hysterectomy

Case Report

A 76-year-old female was admitted with a 6-week history of haematuria. She also gave a history of hourly frequency of micturition for approximately 2 years, but had experienced no dysuria. She had felt generally unwell for several months prior to admission. Three years previously, she had undergone abdomino-perineal excision of the rectum with total hysterectomy for adenocarcinoma of the middle third, extending downwards towards the anal margin and infiltrating the uterus and upper third of the vagina. Examination under anaesthesia was performed, when a large stone, measuring 10 x 4 cm was found to be lodged in the vagina (Fig.). The vagina was found to be otherwise normal with no narrowing of the introitus. The vestibule was noted to be rather deeply situated, so that with the patient supine, any urine escaping from the urethra would tend to run downwards towards the vaginal orifice. Cystoscopy revealed a small capacity bladder with diffuse cystitis. On distending the bladder with water, no fistulous leak into the vagina could be demonstrated.

Subsequent analysis showed the stone to be composed of calcium phosphate and ammonium salts.

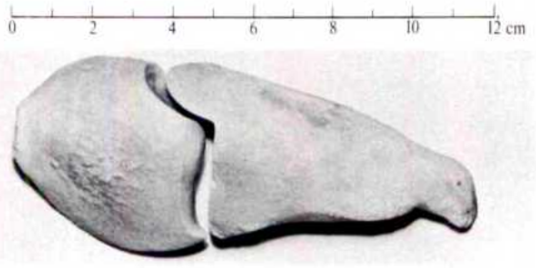

Fig.

Comment

Vaginal stones have been described as occurring as a result of the deposition of urinary salts in the vagina, either as a primary phenomenon or, secondarily, due to the presence of an intravaginal foreign body or to ulceration of a bladder stone through the vesico-vaginal septum.

Stansfield (1942) detailed the following conditions necessary for the formation of primary vaginal calculi: (*a*) urinary leakage into the vagina through a vesico-vaginal fistula, (*b*) the presence of a congenital or acquired vaginal stenosis.

Miller (1973) described a primary vaginal calculus occurring in a 17-year-old severely retarded girl in which neither of these conditions existed. He postulated that the calculus was formed as a result of urinary contamination of the vagina in association with incontinence and the prolonged maintenance of a recumbent posture, and reviewed 3 similar preceding cases.

In the case described, although there was no evidence of visico-vaginal fistula or of vaginal stenosis, it was felt that, in association with her marked degree of frequency, there was probably some element of urinary inconsistence. The abnormally deep situation of the urethral orifice was thought to be the result of intrapelvic fibrosis and contracture subsequent to her A-P resection and total hysterectomy. In the supine position, the result would be a tendency for urine to pool at the introitus, causing leakage into the vagina and the gradual deposition of urinary salts to form a primary vaginal calculus.

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Stansfield, F. R. (1942). Vaginal calculus. *J. Obstet. Gynaecol. Brit. Emp.*, **49**, 82.

Miller, N. (1973). Primary vaginal stones. *Obstet. Gynaecol.*, **41**, 459-60.

The Author

R. M. Weaver, Dudley Road Hospital, Birmingham.

British Journal of Urology (1979), 51, 235

Conferences and Courses

18th Congress of the International Society of Urology

Paris. 24-29 June 1979.

Further particulars from: Professor Alain Jardin, Congrès Urologie, P.M.V., B.P. 246, 92205 Neuilly Sur Seine, France.

International Conference on Urinary Calculi

Perth, Western Australia. 4-8 August 1979.

The Conference will include sessions on: Theories of Stone Formation, The Epidemiology of Stone Diseases, Metabolic Inter-relationships, Medical and Surgical Treatment, Prevention of Stone Formation.

Further information from: Assoc. Professor J. G. Brockis, International Conference on Urinary Calculi, University Department of Surgery, Royal Perth Hospital, Box X2213, G.P.O., Perth, Western Australia 6001.

Special Aspects of Urology

University of Liverpool and Liverpool Regional Urological Centre. 23-29 September 1979.

The course will include sessions on: Management of Renal Failure, Chronic Infections, Vesicourethral Neuropathy, Technical and Scientific Developments in Urology, Paediatric Urology, Male Infertility. Distinguished guest speakers will take part and the course is approved under the Advanced Postgraduate Training Scheme for senior trainees and consultants. (Under this Scheme, fees and expenses will be reimbursed as agreed by the Department of Health and Social Security and Regional Medical Officer in the case of eligible applicants.)

Further information from: Mr N. O. K. Gibbon, c/o Postgraduate Office, 1st Floor, Duncan Buildings, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XW.

First International Congress on Hormones and Cancer

Rome, Italy. 4-6 October 1979.

Further information from: Professor S. Iacobelli, Laboratorio di Endocrinologia Molecolare, Instituto di Clinica Obstetricia e Ginecologica, Universita Cattolica, Via Pineta Sacchetti 644, I-00168 Roma.

Congress of the Hungarian Society of Urology and Nephrology

Budapest, Hungary. 10-13 October 1979.

Further information from: Dr I. Soltesz, Department of Urology, University of Debrecen, H-4012 Debrecen.

31st Meeting of the German Society for Urology

Munich, Germany. 17-20 October 1979.

Further information from: Dr Hartung, Urologische Klinik und Poliklinik, Ismaninger Strasse 22, 8000 Munich 80, Germany.

Annual Meeting of the Swiss Society for Urology

Biel, Switzerland. 8-10 November 1979.

Further information from: Prof. Dr K. Bandhauer, Urologische Klinik Kantonsspital, CH-9007 St Gallen.

International Symposium. Current Treatment of Urethral Stricture in Man

Vienna, Austria. 23-24 November 1979.

Further information from: Dr P. Porpaczy, c/o Wiener Medizinische Akademie, Alser Strasse 4, A-1090 Wien.

Organisers wishing to have details of their courses and conferences published in the Journal should send details to J. E. Newsam, Western General Hospital, Edinburgh EH4 2XU.

British Journal of Urology (1979), 51, 236

Conversion Table—S.I. units

Old units			*Conversion factor multiply by:*		*S I units*	
Constituent	*Normal range*	*Units*	*Old to new*	*New to old*	*Normal range*	*Units*
Venous blood						
Albumin	3 5-5.5	g/100 ml	10	0.1	35-55	g/l
Bicarbonate (total)	24-30	mEq/l	1	1	24-30	mmol/l
Bilirubin	0.1-0.8	mg/100 ml	17	0.059	2-14	µmol/l
Calcium	8.6-10.5	mg/100 ml	0.25	4	2.15-2 65	mmol/l
Chloride	100-107	mEq/l	1	1	100-107	mmol/l
Cholesterol	140-240	mg/100 ml	0.026	38.5	4.0-6.5	mmol/l
Creatinine	0.6-1.4	mg/100 ml	88	0.0114	55-125	µmol/l
Glucose	65-95	mg/100 ml	0.056	18	3.5-5 5	mmol/l
Iron	110-130	µg/100 ml	0.18	5.6	circa 20	µmol/l
Magnesium	1.4-1.8	mEq/l	0.5	2	0.70-0.90	mmol/l
Phosphate	2.5-4.5	mg/100 ml	0.32	3.1	0.8-1.4	mmol/l
Potassium	3.8-5.2	mEq/l	1	1	3.8-5.2	mmol/l
Protein (total)	6 5-8.0	g/100 ml	10	0 1	65-80	g/l
P.B.I.	3.75-7.5	µg/100 ml	79	0.0127	300-600	nmol/l
IgG	500-1600	mg/100 ml	0.01	100	5.0-16.0	g/l
IgA	125-425	mg/100 ml	0.01	100	1.25-4.25	g/l
IgM	50-180	mg/100 ml	0.01	100	0.5-1.8	g/l
Sodium	136-149	mEq/l	1	1	136-149	mmol/l
Transferrin	150-300	mg/100 ml	0.01	100	1.5-3 0	g/l
Triglyceride	60-140	mg/100 ml	0.0113	88 5	M2.0 P<1.5	mmol/l
Uric acid	2-7	mg/100 ml	0.06	16 7	0.1-0.4	mmol/l
Urea	15-40	mg/100 ml	0 17	6.0	2.5-6.5	mmol/l
Arterial blood						
Base excess	−3-+3	mEq/l	1	1	−3-+3	mmol/l
PCO_2	32-46	mmHg	0.135	7 5	4.5-6.0	kPa
PO_2	80-100	mmHg	0.133	7 5	10.5-13.5	kPa
Urine outputs/24 h						
Calcium	200	mg	0 025	40	5	mmol
Creatinine	1-2	g	8 8	0.113	9-18	mmol
5H1AA	3-17	mg	5 23	0.19	16-90	µmol
Inorganic P.	1000	mg	0 032	31	30	mmol
Magnesium	100	mg	0 041	24	4.2	mmol
Potassium	70	mEq	1	1	70	mmol
Protein	<0.05	g	1	1	<0.05	g
Sodium	200	mEq	1	1	200	mmol
Urea	25	g	17	0.06	400	mmol
Uric acid	500	mg	0.006	167	3.0	mmol
VMA	<7	mg	5 05	0.2	<35	µmol

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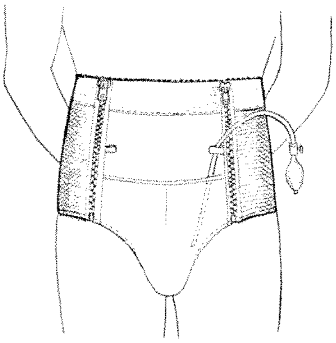

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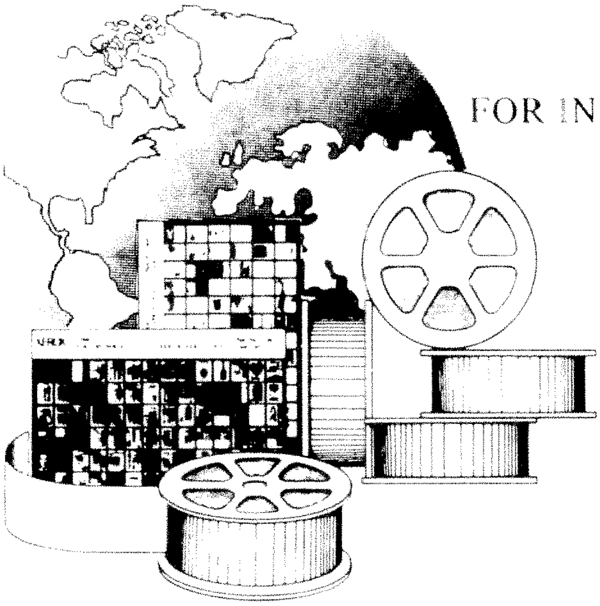

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CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which the papers are published in the *Journal, i.e.* in anatomical order beginning with papers on the Adrenal.

A general section is included at the end.

ADRENAL

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KIDNEY

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Report on work of All Union symposium on state of kidneys under external conditions. (Leningrad, March 1976.) (B. B. Bondarenko.) *Ter. Arkh.* 1978, **50**, 150.

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Adult hemolytic uremic syndrome with renal arteriolar deposition of IgM and C_3. (S. P. Hammar *et al.*) *Am. J. Clin. Pathol.* 1978, **70**, 434.

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Prevention in general practice: what is dangerous for the kidney and its function? (R. Heidler.) *Forstchr. Med.* 1978, **96**, 2203.

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[1] Titles in this list have been taken from those listed in *Current Contents: Clinical Practice* published by Institute for Scientific Information, Philadelphia.

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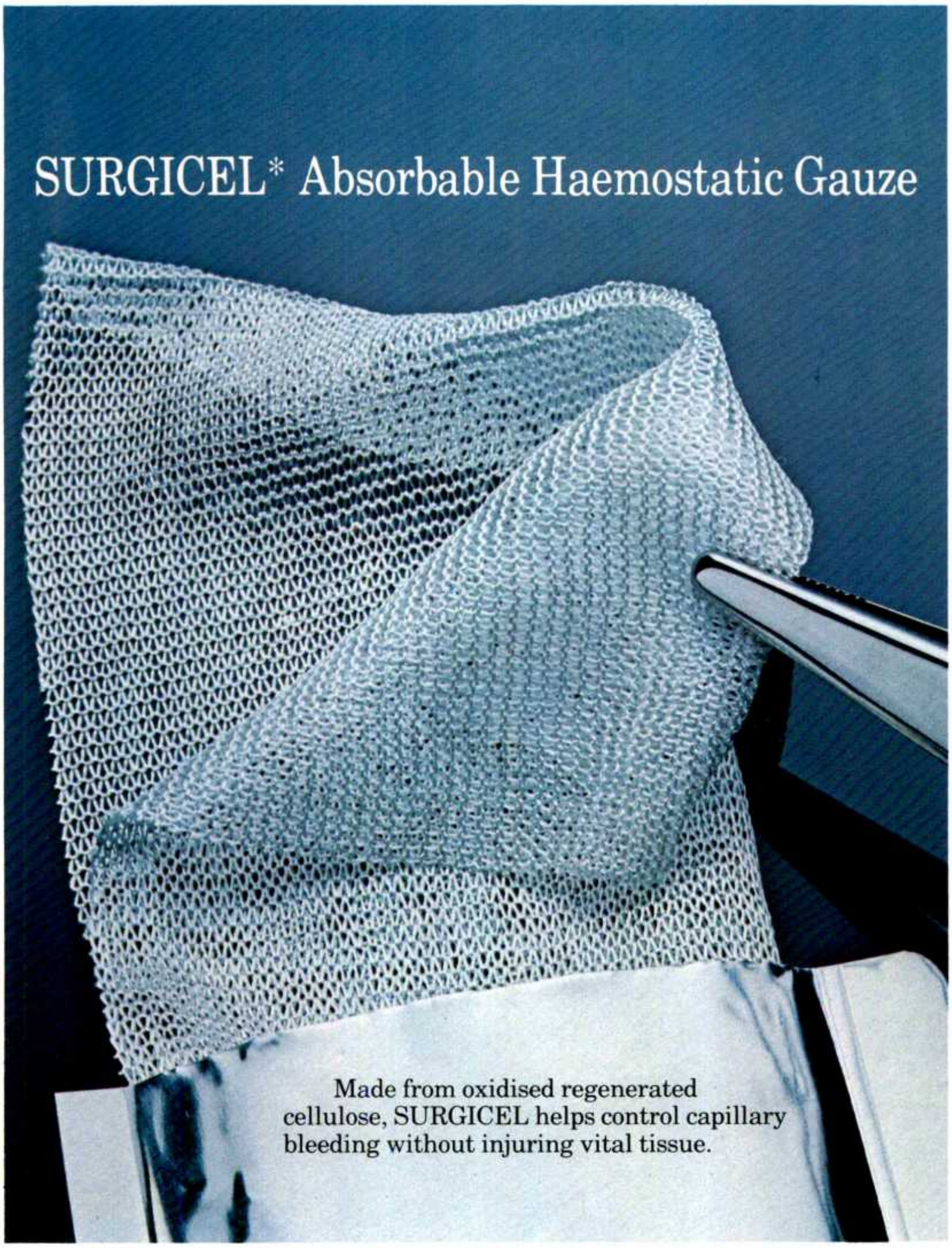
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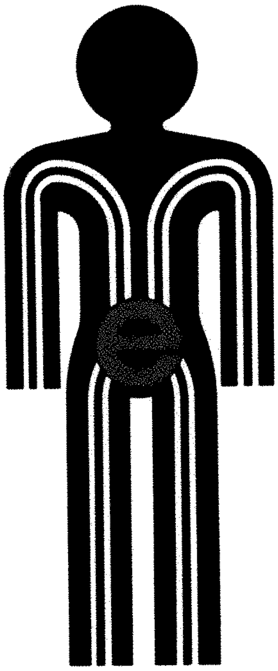

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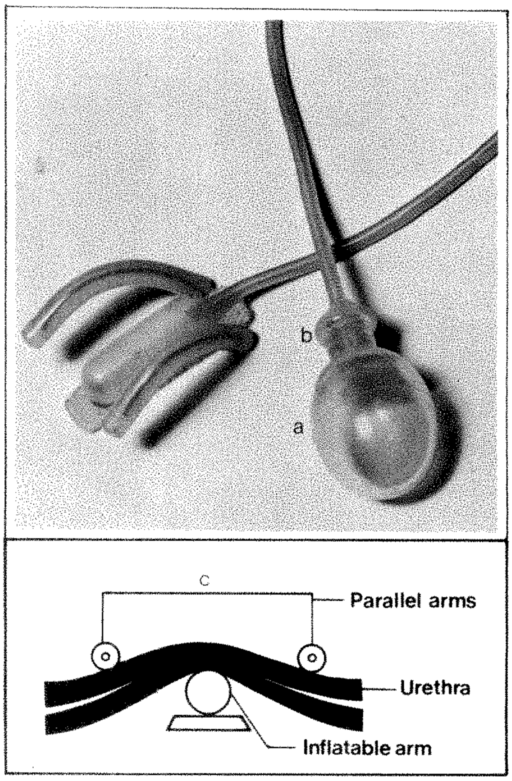

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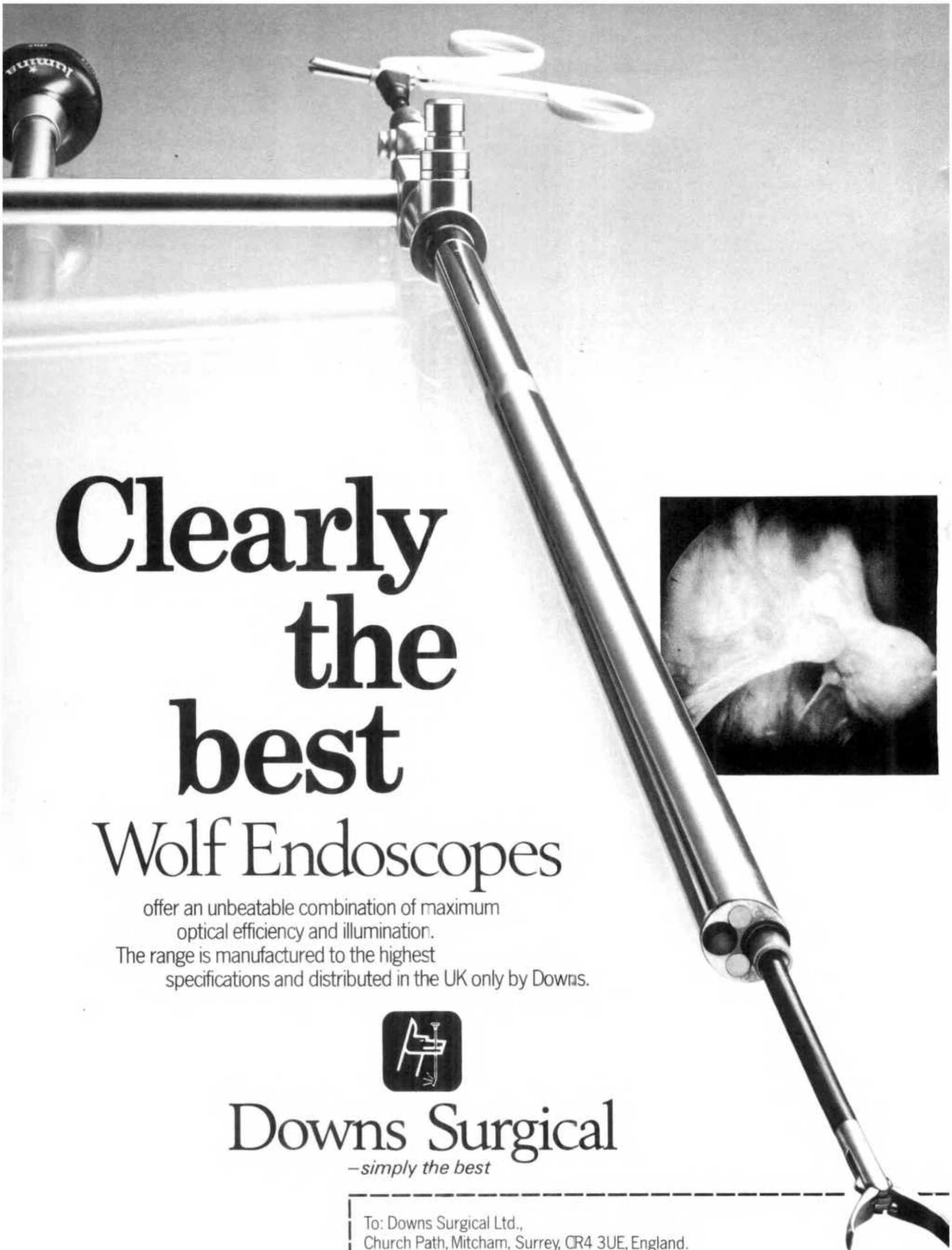

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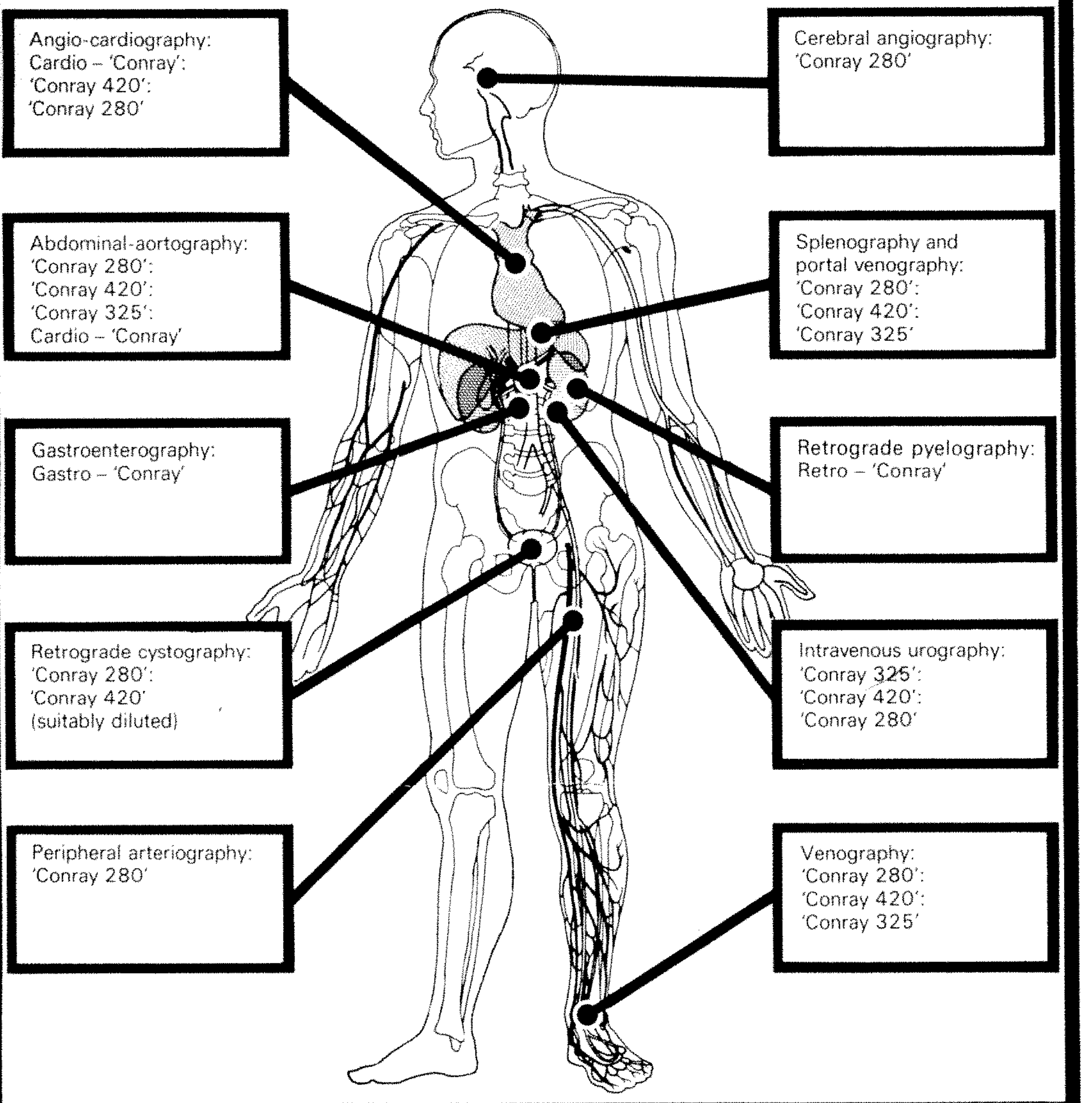
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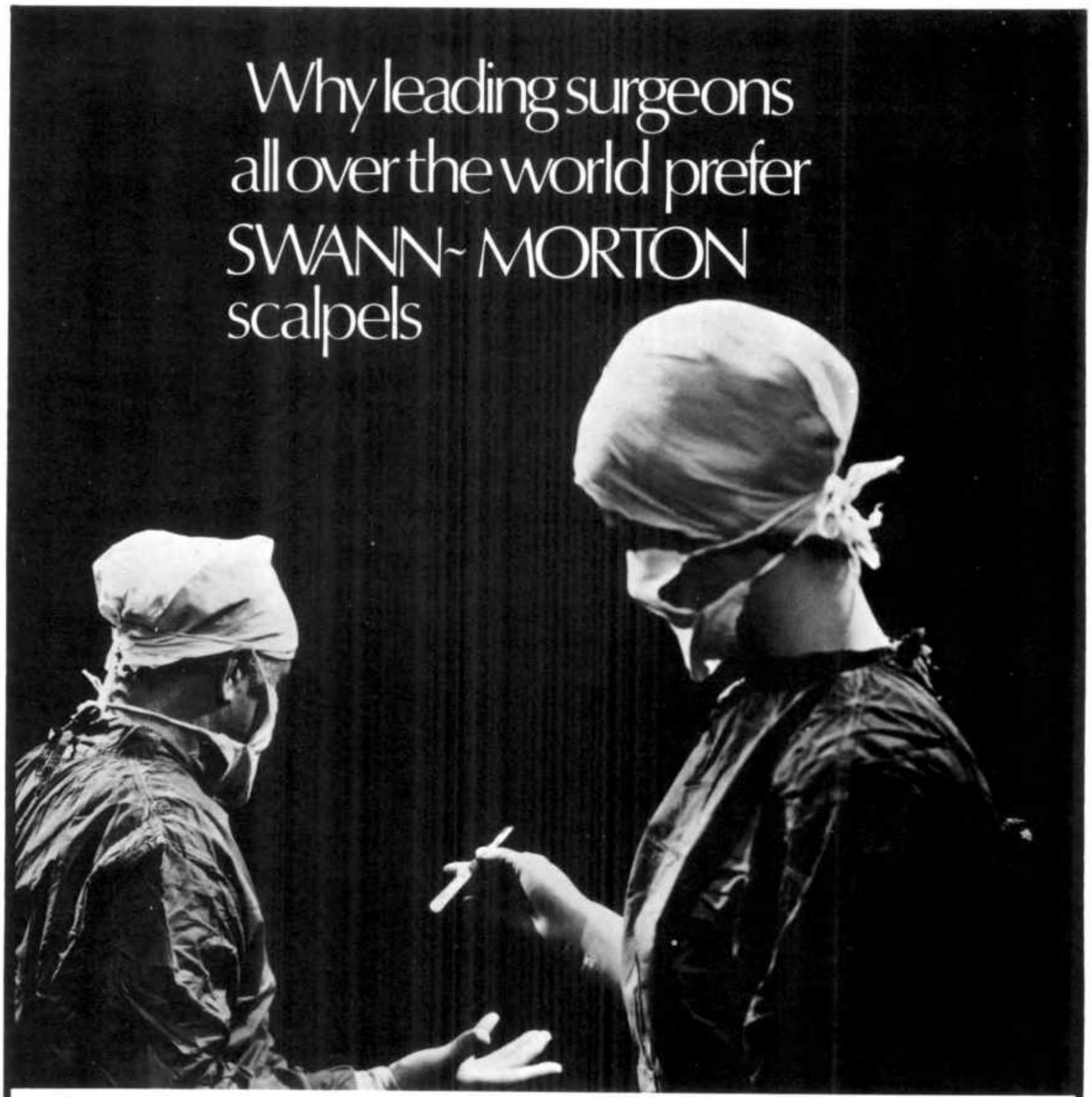
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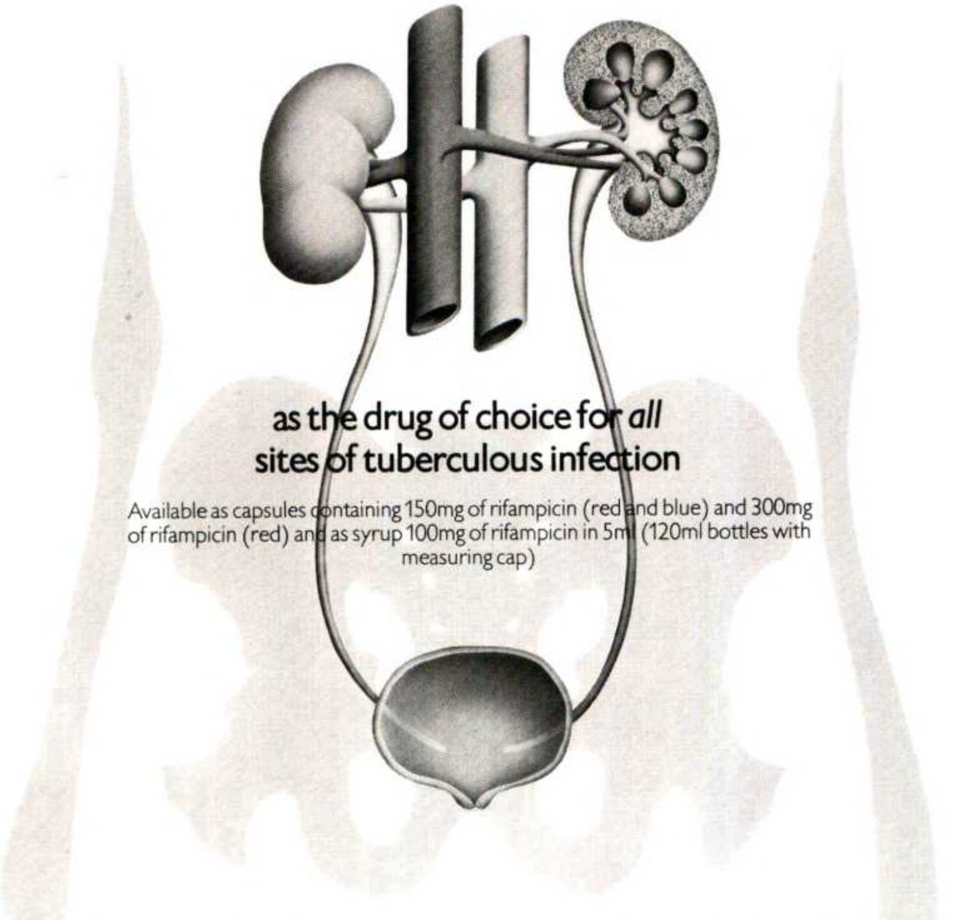

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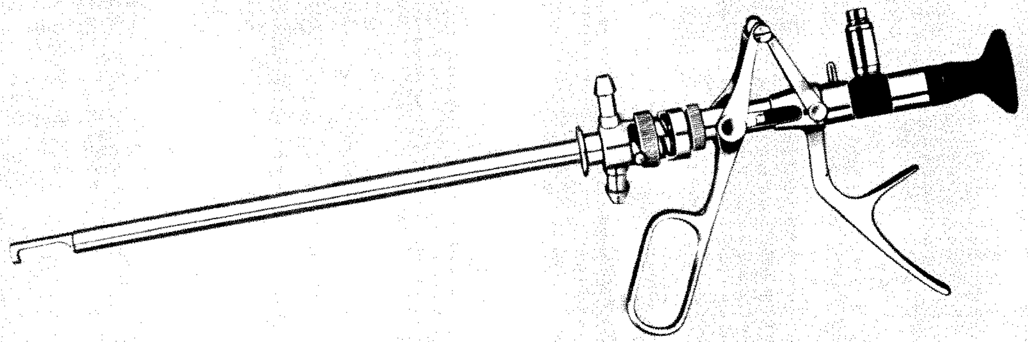

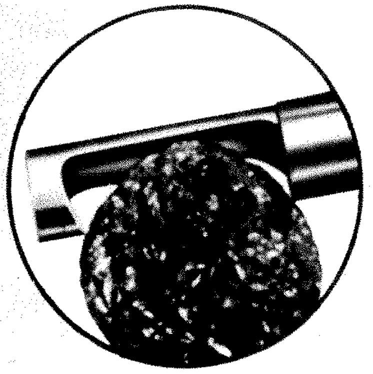

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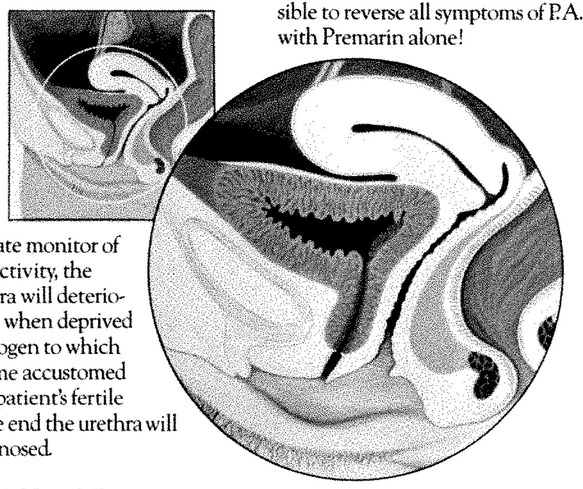
Older women presenting with frequency, urgency and painful micturition often describe their condition as 'cystitis'. There can hardly be a woman in existence who has not suffered the transient discomfort of a 'simple cystitis' at some time in her early life, but as she reaches middle age, although the symptoms may appear to her as the same, the cause, particularly in the absence of infection, may be atrophic changes in the distal urethra responding to hormonal disparities of the menopause.[1]

Untreated, these atrophic changes can be devastating and demoralising in their effect.[2]



A delicate monitor of oestrogen activity, the distal urethra will deteriorate rapidly when deprived of the oestrogen to which it has become accustomed during the patient's fertile years. In the end the urethra will become stenosed.

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3. Frank urinary tract infection should of course be treated with appropriate antibiotics or urinary anti-infectives.

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However in patients with a longer history of frequency and urgency, if oestrogen therapy does not effect a rapid and complete elimination of symptoms then the possibility of a secondary urethral stenosis should be considered.

References:
1. Willington, F. L. The Practitioner. 220, 739, 1978.
2. Smith, P. J. B., Ayerst Medical Library Vol. 2, No 2, 1978.
3. Smith, P. J. B., The Practitioner, 218, 97, 1977.

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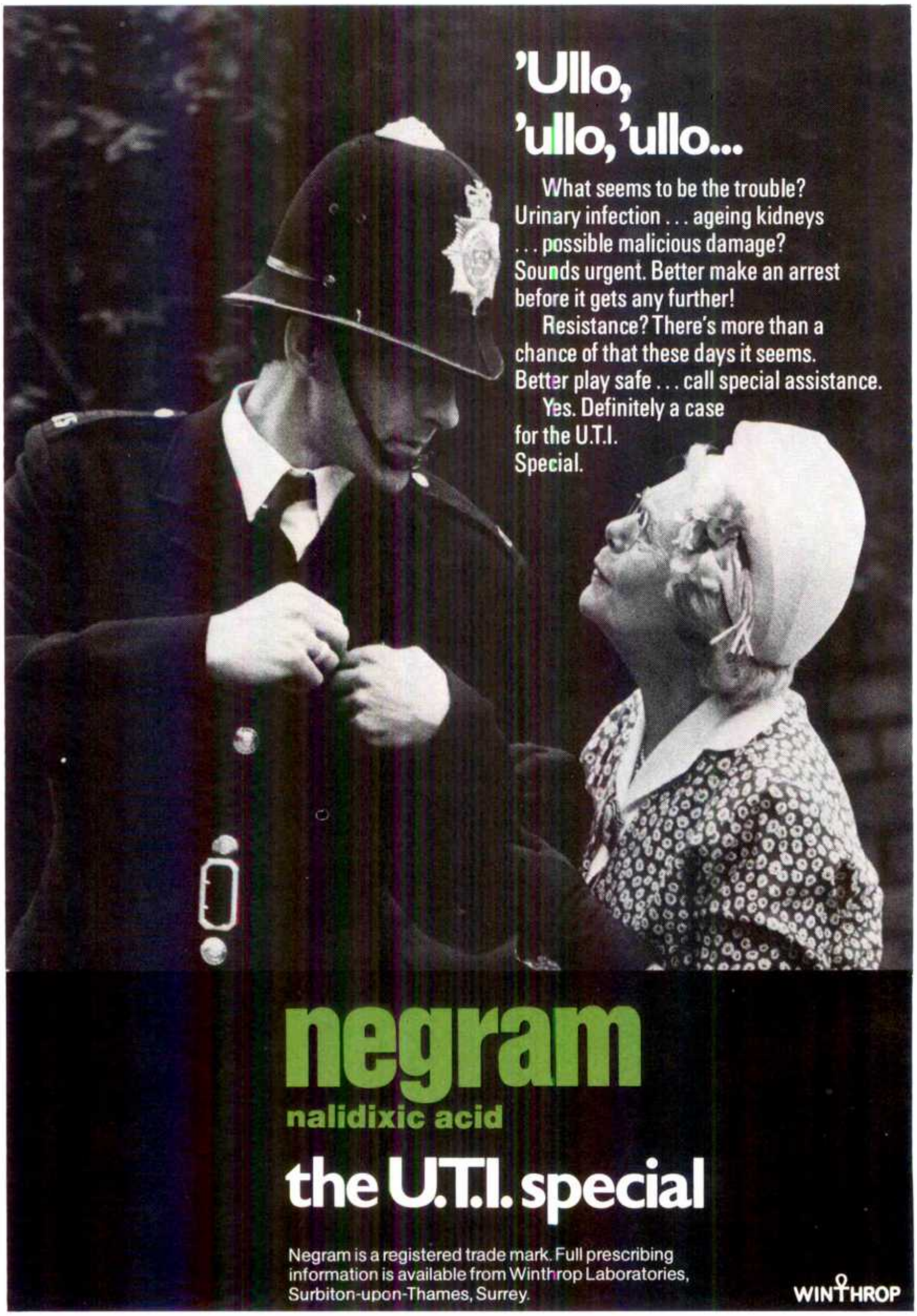

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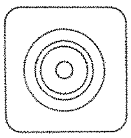

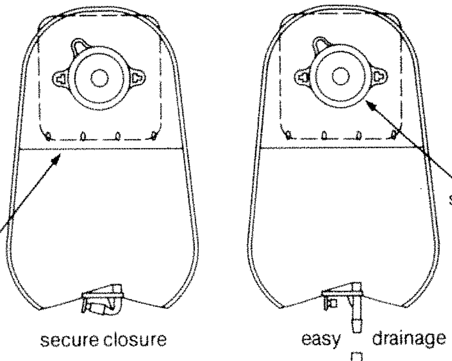

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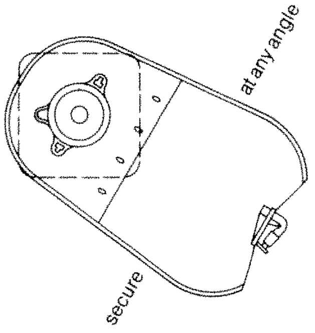

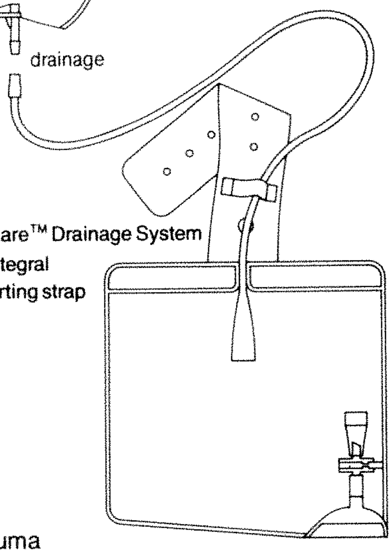

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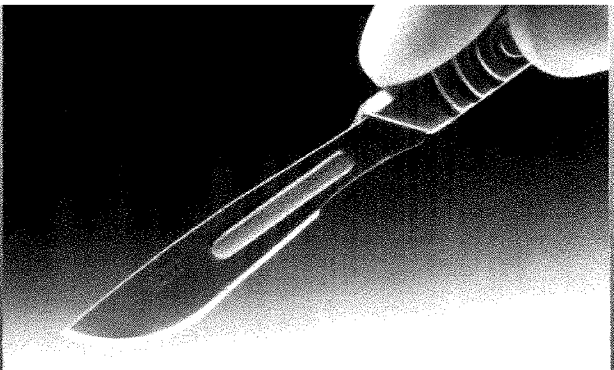

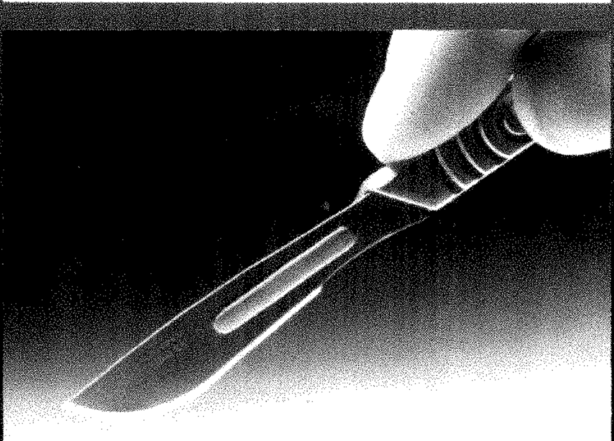

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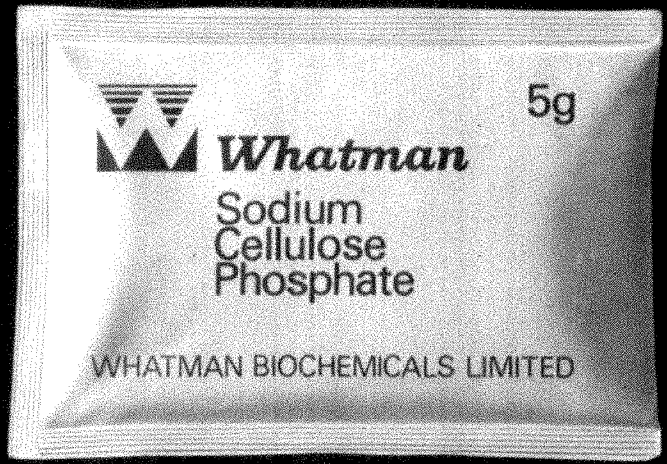

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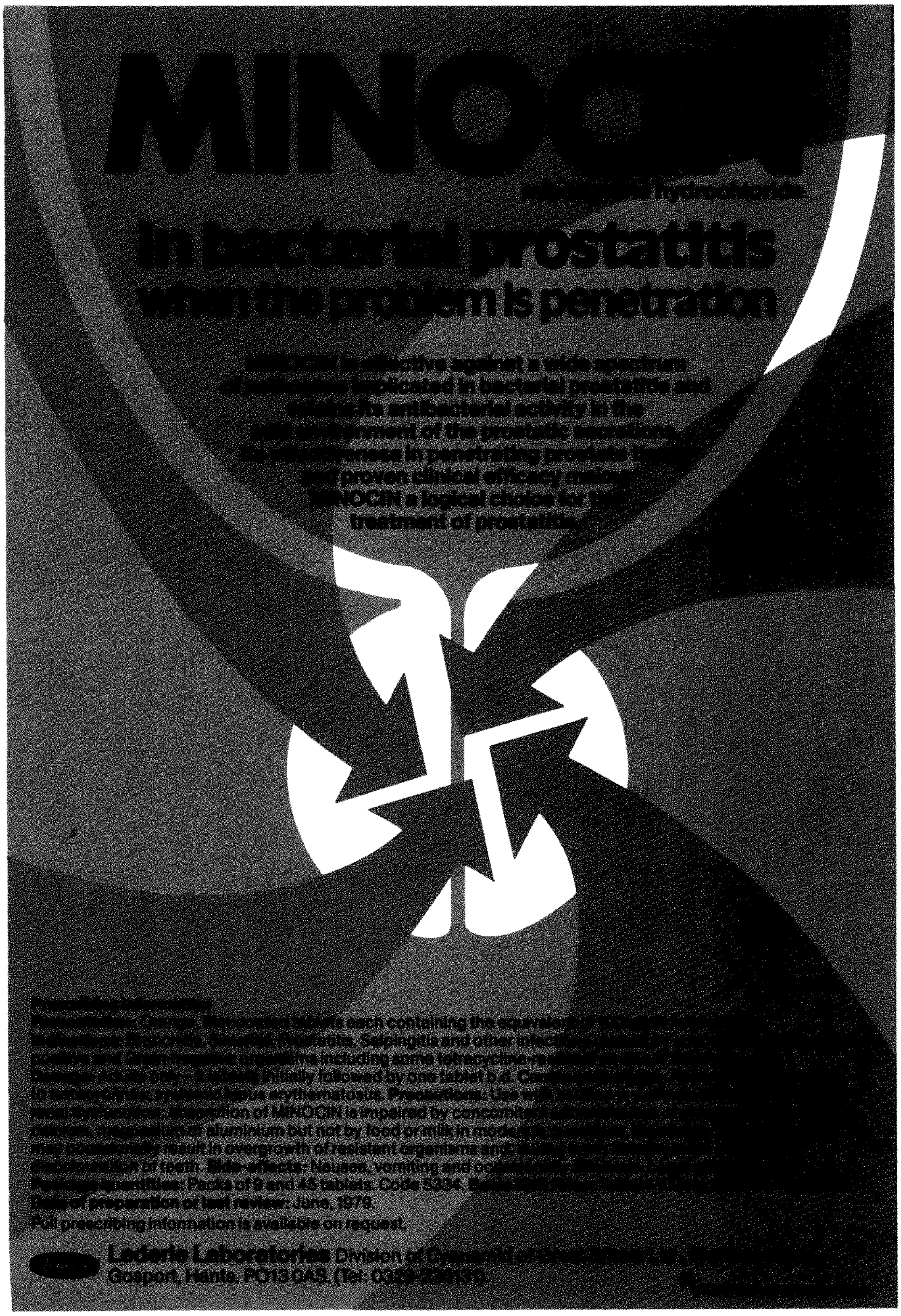

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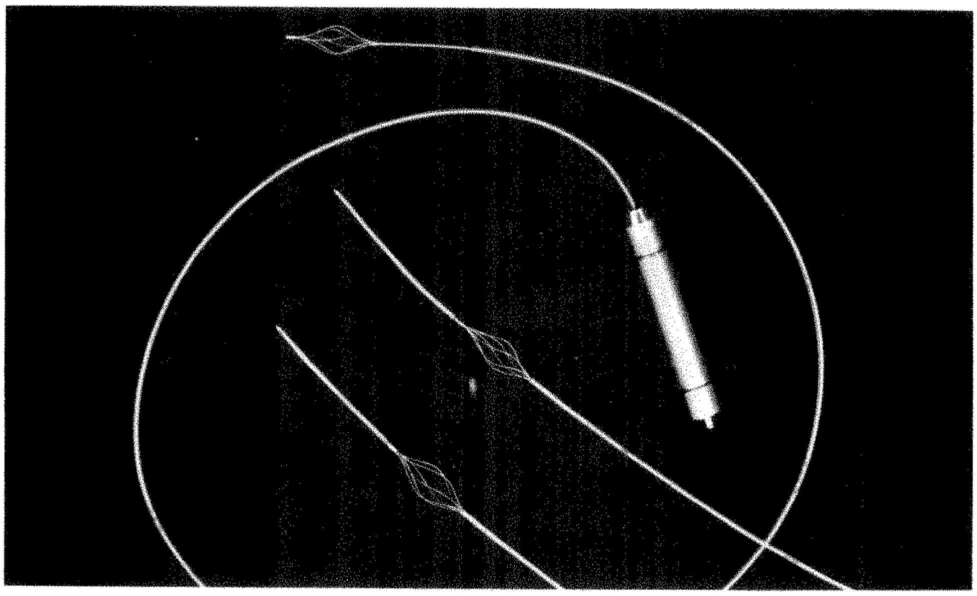

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Genitourinary Tuberculosis: A 7-Year Review

J. G. GOW

Department of Urology, Wrightington Hospital, Wigan

Summary—Since 1970 short course regimes of chemotherapy have been adopted for the treatment of 87 patients suffering from genitourinary tuberculosis. The response to chemotherapy, the effect of surgery, the importance of hypertension and the relapse rate have been studied. It is concluded that all cases of genitourinary tuberculosis will respond to a short intensive course of chemotherapy, which need not be given for longer than 6 months.

Thirty-five years have passed since the discovery of streptomycin, the first great milestone in the chemotherapeutic treatment of tuberculosis, as it heralded the start of a new era in the management of a disease which at that time was often fatal. This inspired research was followed in 1952 by the even more important discovery of isoniazid and later, in 1955, by the appreciation that combined chemotherapy with streptomycin, isoniazid and para-aminosalicylic acid (PAS) not only prevented the emergence of resistant strains of organisms but, if given continuously for a prolonged period of time (2 years or more), controlled the disease in almost 100% of cases.

The next milestone did not occur until 1966, when rifampicin was discovered, later to be followed in the early 1970s by what is unquestionably the greatest milestone, the acceptance of short course chemotherapy as the standard method of treatment of tuberculosis.

This paper is a review of 87 cases of genitourinary tuberculosis treated between 1970 and 1977 by short course regimes of chemotherapy.

Patients and Methods

Eighty-seven patients suffering from genitourinary tuberculosis were treated between January 1970 and December 1977. Fifty-four were male and 33 female. The average age of the males was 45 and the females 41; the oldest patient was 73 and the youngest 16.

The presenting symptoms and signs are shown in Table 1. The patients were divided into 2 groups; the first group, which numbered 61, was treated between 1970 and 1974 and the regimes of treatment employed are summarised in Table 2. All of these patients were admitted to hospital for the first 3 months of treatment, after which they were supervised at out-patient clinics. The second group, which numbered 26, was treated by the regime detailed in Table 3. The patients in this group were all treated as out-patients from the start of chemotherapy, unless individual circumstances made this impossible. They were seen at weekly intervals in the out-patient department, when liver function tests were carried out and a specimen of urine inspected. As rifampicin turns the urine orange, this was a simple way of confirming that the patients were taking their drugs.

Table 1 Presenting Symptoms and Signs

Calcification	45
Frequency	42
Nocturia	37
Dysuria	30
Haematuria	18
Swollen testis	15
Hypertension	14
Stones	4
Sterile pyuria	4
Non-specific infections (*B. coli*)	3

Table 2 Regime of Treatment Between 1970 and 1974 (61 Patients)

Daily	Rifampicin 450 mg Isoniazid 300 mg Ethambutol 800 mg	3/12
Followed by		
Daily	Rifampicin 450 mg Isoniazid 300 mg	4-6-9/12

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Table 3 Regime of Treatment Between 1975 and 1977 (26 Patients)

Rifampicin 600 mg	daily for 2/12
Isoniazid 300 mg	
Pyrazinamide 1 g	
Vit. C 1 g	
Followed by	
Rifampicin 900 mg	twice a week for 4/12
Pyrazinamide 1.5 g	
Vit. C daily for 4/12	

The liver function tests were carried out as all of the 3 drugs used in the primary treatment are metabolised in the liver and it was therefore a possibility that some liver insufficiency might occur. All patients were classified in severity according to the Semb classification (Table 4). A previous history of tuberculosis was obtained from 23 patients (Table 5). In only 2 cases was the genitourinary lesion associated with an acute tuberculous infection of other systems, both being combined with a pulmonary lesion. In 12 patients the tuberculous disease occurred more than 20 years before the genitourinary lesion was diagnosed. Forty-five patients (52%) presented with calcification, which shows an increasing trend in this complication when compared with previously reported series (Gow, 1965; Antonio and Gow, 1975). Two patients developed calcification 2 years after completing treatment. Fourteen patients were found to have hypertension (a systolic pressure of over 180 mmHg and a diastolic pressure of more than 100 mmHg).

In 71 patients the disease as assessed radiologically and clinically was localised to the kidney, in 12 males to the male genital system and in 4 the whole urinary tract was involved.

Investigations

The diagnosis was confirmed on isolating mycotuberculosis on artificial culture media and no treatment was started until an organism was isolated, unless there was overwhelming clinical evidence of the disease. Inoculation of the urine into guinea pigs was only very rarely required. An intravenous urogram was always carried out using the high dose technique and was followed by a cystoscopy. Twenty of the 87 patients had a small capacity bladder and 31 an abnormal ureteric orifice. As the high dose technique for intravenous urography was used, retrograde pyelography was rarely necessary and in this series was carried out on only 6 occasions. Repeated urine analyses were performed during the course of treatment to exclude a superimposed non-specific infection. The diagnosis was not considered as often as it might have been as 4 cases in this series were diagnosed only after surgery, one following nephrectomy, another after a transurethral resection of the prostate and the last 2 following orchiectomy for persistent epididymo-orchitis.

Table 4 Semb Classification in 87 Patients

		Patients
Semb 1	Tuberculous bacillus or small caliceal deformity with or without genital lesion	15
Semb 2	Ulcerocavernous lesion affecting one or more calices	42
Semb 3	Extensive renal tuberculosis involving the major part of one or more calices	30

Table 5 Previous Tuberculosis History (23 Patients)

Lungs	10
Joints	5
Genitourinary	3
Spinal	3
Miliary	1
Cervical lymph nodes	1

Operative Procedures (Table 6)

Nephrectomy is still advocated as an important part of the suggested management and is performed when the kidney is non-functioning or is so badly diseased that any return to useful function is impossible. It is suggested that all surgical procedures should be carried out during the initial 2-month period of intensive continuous chemotherapy. The management of obstruction at the lower end of the ureter demands careful supervision. The present policy is to take one 17 × 14 inch film urogram at 2-weekly intervals after the start of chemotherapy. If, after a month, there is no improvement, prednisolone 20 mg tds is added to the chemotherapy. If the ureter remains un-

Table 6 Surgical Procedures

Excisional		*Conservative*	
Nephrectomy	23	Augmentation of bladder	9
Epididymectomy	8	Reimplantation of ureter	11
Partial nephrectomy	6		
Epididymectomy and nephrectomy	2		

changed after a further month, reimplantation into the bladder by means of a reflux-preventing technique is recommended.

Follow-up Period (Table 7)

As no patient has relapsed during this period of time it is suggested that it is unnecessary for any patient to be followed up for more than a year after the course of chemotherapy has been completed. It is no longer reasonable to expect all patients to be followed up indefinitely in case one should relapse. What Fox (1977) calls the unacceptable consequences of perfectionism is relevant. Patients should be instructed to seek medical advice if their urinary symptoms recur and the suggestion by Wechsler and Lattimer (1975) that patients should be followed up indefinitely is untenable in the light of modern experience.

Table 7 Follow-up of Patients by Years

0.5-1	18
1-2	16
2-3	16
3-4	18
4-5	10
5-6	4
6-7	4

Results

Symptomatic improvement was rapid after chemotherapy was commenced and most of the patients became symptom-free within 4 to 6 weeks of the start of treatment. The exceptions were patients with a small contracted bladder, who required bladder augmentation. The urine of all patients was sterile at the end of the initial 2 months' chemotherapy and there have been no relapses.

There were 4 deaths in this series, all associated with caecocystoplasty. The first was due to a ruptured aortic aneurysm 2 weeks after surgery and the second to a myocardial infarction 2 years later; the third was caused by renal failure 15 months after surgery and the pathology of the fourth was a carcinoma of the bladder which appeared 5 years after the bladder augmentation.

Surgical procedures were always carried out during the first 2 months of treatment and there was no operative mortality. Four patients with ureteric obstruction who were given prednisolone showed no improvement and were treated by reimplantation of the ureter into the bladder.

All operations were carried out under a screen of chemotherapy which was continued until the patient was discharged from hospital, even though the first 2 months of chemotherapy had been completed.

Hypertension

Three patients showed a marked improvement after surgery, one after reimplantation of the ureter, one after nephrectomy and the third after caecocystoplasty. All 3, however, relapsed within 2 years. Two patients improved without relapse with chemotherapy, 2 became worse and 7 showed no change at the end of treatment.

Toxicity (Table 8)

Renal failure appeared in one patient after one month's intermittent treatment with rifampicin and isoniazid following 3 months' treatment with rifampicin, isoniazid and ethambutol, but recovery was complete after the drugs were stopped. A short period of peritoneal dialysis was required. Ethambutol was replaced in all of the cases that developed toxic reactions.

Table 8 Toxic Effects of Drugs

Isoniazid	*Rifampicin*		*Ethambutol*	
None	Renal failure	1	Leucopenia	1
	Colitis	1	Disturbance of vision	1
			Rash	2
			Severe gastroenteritis	1

Discussion

Short Courses of Chemotherapeutic Treatment

The evidence justifying short course regimes has been provided by prolonged trials on patients suffering from pulmonary tuberculosis, but there is no reason to believe that the genitourinary manifestation should respond differently. Indeed, there are good reasons why the results may be even better. In the first place, fewer bacilli are usually found in renal lesions than in the pulmonary disease. Secondly, Acocella (1967) showed that there was a high concentration of rifampicin in the urine even up to 12 hours. There is additional evidence that isoniazid and streptomycin penetrate into pulmonary cavities (Canetti and Grumbach, 1956; Bartmann and Freise, 1963), that isoniazid and streptomycin penetrate into bone and joints (Debaumont *et al.*, 1965), that

Table 9 Concentration of DDS, Rifampicin, Isoniazid and Pyrazinamide in the Plasma, Ultrafiltrate and Sciatic Nerve of the Dog and Sheep (g/ml or g/g)

Drug	*Species*	*Dose (mg/kilo)*	*Plasma ultrafiltrate at 8 h*	*Sciatic nerve at 8 h*
DDS	Dog	15	3.6	16.8
	Sheep	20	4.1	10.7
Rifampicin	Dog	20	1.5	4.4
	Sheep	50	1.1	1.3
Isoniazid	Dog	15	2.9	6.2
	Sheep	30	6.8	6.4
Pyrazinamide	Dog	50	20.8	20

(Allen *et al.*, 1975).

isoniazid and rifampicin penetrate into renal cavities and that dapsone isoniazid, rifampicin and pyrazinamide penetrate into nerve tissue (Allen *et al.*, 1975) (Table 9). With this circumstantial evidence it was reasonable to presume that there would be a good penetration of isoniazid, rifampicin and pyrazinamide into highly vascular renal tissue and that treatment would be satisfactory. This was confirmed by earlier reports (Kurth and Sulmoni, 1972; Gow, 1976).

Between 1955 and the late 1970s, the continuous 2-year courses of single dose treatment with streptomycin, PAS and isoniazid was highly successful and was considered the standard regime of chemotherapy. However, such courses had disadvantages as they had to be given for a prolonged period, were expensive and demanded extensive resources which taxed the demands of both patients and supervisors. These demands were quite beyond the developing countries, so that it was imperative that simpler, equally effective but less expensive regimes should be found. Many combinations of drugs were tried over a short period of time; all failed because of an unacceptable incidence of resistant organisms, the result of the patients having taken the drugs for an insufficient length of time. One of the first successful clinical trials was reported by the Singapore Tuberculosis Services (1974). This, however, had been preceded by extensive experimental work in the mouse (Grosset, 1978). In this study a group of patients was given streptomycin and isoniazid for 6 months followed by isoniazid alone for 12 months. There was only one bacterial failure after 12 months and there were no further failures over a period of 3 years. Shortly afterwards rifampicin was introduced and this seemed to provide the final evidence and justification for introducing carefully controlled short course regimes. This resulted in the extensive East African/British Medical Research Council studies (1977) which showed that the 6-month regime produced substantially the same results as the standard 18 months' therapy, a finding which was particularly important for developing countries.

When the short course regimes were first introduced in 1970, ethambutol was the third drug used with isoniazid and rifampicin, as this was the combination that gave satisfactory results in the trials conducted on patients with pulmonary disease. It was not an ideal drug and in 1975 was replaced by pyrazinamide as toxic symptoms were seen in a few patients; in addition, there was evidence (Fox and Mitchison, 1975) that pyrazinamide was a bactericidal drug which was more potent than ethambutol, which was only bacteristatic, although it was likely to be more toxic. Further evidence was forthcoming that the addition of pyrazinamide to rifampicin and isoniazid-containing drug regimes produced a significantly more rapid sputum conversion. Pyrazinamide first came into disrepute because of its hepatoxicity and it was largely abandoned. This toxicity was dose-related and it was because 2 g or more were being used that the problems with toxicity occurred. Now that the dose is kept much lower no reactions with pyrazinamide have been experienced.

Dose

The one-dose method was selected as it was recognised by some authorities that a single daily dose was more effective than one given twice daily in 2 equally divided amounts, as in this way it inhibited bacterial multiplication for several days. This effect was caused by the high peak concentration which inhibited mutant bacilli with a low degree of resistance (Selkon *et al.*, 1964).

It was a method much appreciated by the patients, who found it the easiest way to be certain that the drugs were taken regularly.

Choice of Rifampicin and Pyrazinamide for Follow-on Course

Fox (1977) pointed out that there is *in vitro* and *in vivo* evidence that rifampicin and pyrazinamide have special sterilising roles in short course chemotherapy—rifampicin because it kills actively dividing bacilli after a shorter period of exposure than any other known drug, while pyrazinamide can eliminate the resting dormant bacilli which reside in macrophages, into which pyrazinamide penetrates easily. It therefore seemed logical to use these 2 drugs to prevent relapse and to destroy any organisms that remained alive after the initial intensive course. The results have confirmed the efficacy of this regime.

Toxicity

Only 2 patients showed any toxicity to rifampicin. One developed renal failure followed by complete recovery; the other developed colitis after 2 months' treatment, but improved after the drug was withdrawn. This patient received no further chemotherapy and has shown no recurrence of the disease nearly 2 years after cessation of treatment.

In all of the patients who developed toxicity to ethambutol the drug was stopped permanently, as early attempts to reintroduce it produced a rapid return of the toxic symptoms. The patient who was treated with ethambutol and who developed leucopenia after only 3 weeks' treatment had no further chemotherapy. He was followed up for 2 years and showed no evidence of recurrence; the disease still appears to be inactive even after such a short course of chemotherapy. There was no toxicity to either isoniazid or pyrazinamide in this series, but recently one patient developed jaundice on the initial 3-drug regime. This slowly disappeared when the treatment was changed to the twice-weekly method.

Surgery

One advantage of genitourinary tuberculosis over the other manifestations of the disease is that surgical treatment is always available and it is mandatory that if the short course regimes are to be accepted, then early surgery must be carried out. After the renal disease has reached a stage where there is no chance of any functional recovery it is most unsatisfactory to suggest prolonged treatment for a functionless, largely avascular organ; early surgery in such cases would remove a serious problem and convert the disease into one of minor character which can be controlled by modern chemotherapy. The results of this approach are vindicated by the absence of any relapses within the 7-year period under review. Strictures at the lower end of the ureter need careful supervision, especially if the patients have been put on cortisone, as one patient developed a relapse of a pulmonary lesion whilst taking steroids. Two patients with an early stricture at the lower end of the ureter improved with chemotherapy and it is our experience that although cortisone may produce dramatic results, it should be used with considerable caution.

Future Developments

All of the evidence now being published suggests that short-term chemotherapy for all manifestations of tuberculosis is the treatment of choice. At the moment 9 months seems the optimum period for the pulmonary disease, but 6 months or less would appear to be adequate when the disease affects the genitourinary system. As the drugs seem to penetrate renal tissue so readily it would be advisable to arrange carefully controlled and analysed clinical trials in an attempt to reduce the second period of treatment from 4 to 2 months. Although the results of the last 2 years have been satisfactory, the clinical evidence now being published indicates that a change in the regime might be an advantage.

The initial 2 months' treatment with isoniazid, rifampicin and pyrazinamide should remain the same, as these drugs are all bactericidal and the addition of pyrazinamide does increase the sterilising effect. Pyrazinamide adds little to the follow-up phase, however, as it is only fully effective if given with isoniazid and rifampicin, and should be replaced by isoniazid. There is also evidence (Hong Kong Chest Service/British Medical Research Council, 1978), that when given thrice-weekly rifampicin and isoniazid produce very few immunological reactions. A trial of rifampicin, isoniazid and pyrazinamide for 2 months followed by 2 months of rifampicin and isoniazid taken 3 times a week should be carried out, for if the course of chemotherapy can be restricted to 4 months this will result in a considerable saving for both the patient and the clinician.

It is suggested that the modern treatment of genitourinary tuberculosis should be 2 months' intensive chemotherapy with rifampicin, isoniazid and pyrazinamide, followed by treatment 2 or 3 times a week with a combination of rifampicin and isoniazid for 2 to 4 months. Surgery, if required, should be performed as an elective procedure about 6 weeks after the start of the triple drug regime. Patients should be followed up for not more than 12 months after the course of chemotherapy is completed, except for patients with renal calcification. They should be treated like any other patient with this condition and followed up for a number of years, until the supervisor is satisfied that the calcification is remaining static and that there is no deterioration in renal function.

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Nephroplasty in the Management of Hydronephrosis

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Summary—Seventeen patients with hydronephrosis were treated by nephroplasty and pyeloplasty. This combination proved to be a simple and effective way of reducing intrarenal dilatation and encouraging dependent drainage from the lower pole calices.

Nephroplasty, or nephroplication, was first described by Stewart (1947) as an operation for the relief of hydronephrosis where the obstruction was associated with an aberrant lower polar vessel.

Nephroplasty involves folding the kidney upon itself in such a way as to bring the upper and lower poles together. This results in drawing the lower pole vessels towards the hilum of the kidney, away from the pelviureteric junction. This procedure, combined with freeing of any adhesions at the pelviureteric junction, gave encouraging results as a primary treatment in some cases of hydronephrosis (Stewart, 1957; Collins *et al.*, 1967; Smith, 1972).

However, in such a situation most urologists would prefer to carry out a formal pyeloplasty, using a disconnection technique to transpose the pelviureteric junction away from any lower pole vessels. For this reason nephroplasty has not established a prominent place in the surgical management of hydronephrosis.

In a study of 100 nephroplasty procedures performed over a 10-year period (Smith, 1972) it became clear that in a group of patients where the pelviureteric obstruction was associated with marked intrarenal dilatation, nephroplasty in combination with pyeloplasty offered an additional bonus in that by compressing the dilated calices it reduced intrarenal dilatation and by elevating the lower pole it encouraged drainage from the lower pole calices.

Because of the marked intrarenal dilatation and associated cortical thinning, this type of hydronephrotic kidney is easy to fold and the more elaborate technique as described by Stewart (1957) proved unnecessary.

Patients and Methods

Combined nephroplasty and pyeloplasty have now been performed on 17 patients over a 6-year period. Their ages ranged from 6 to 46 years. In 9 patients an aberrant lower pole vessel was associated with the hydronephrosis. Twelve of the patients had a Hynes-Anderson pyeloplasty and Culp pyeloplasty was performed in the remaining 5. In all cases the diagnosis was made by intravenous pyelography and on each X-ray marked intrarenal dilatation was clearly evident.

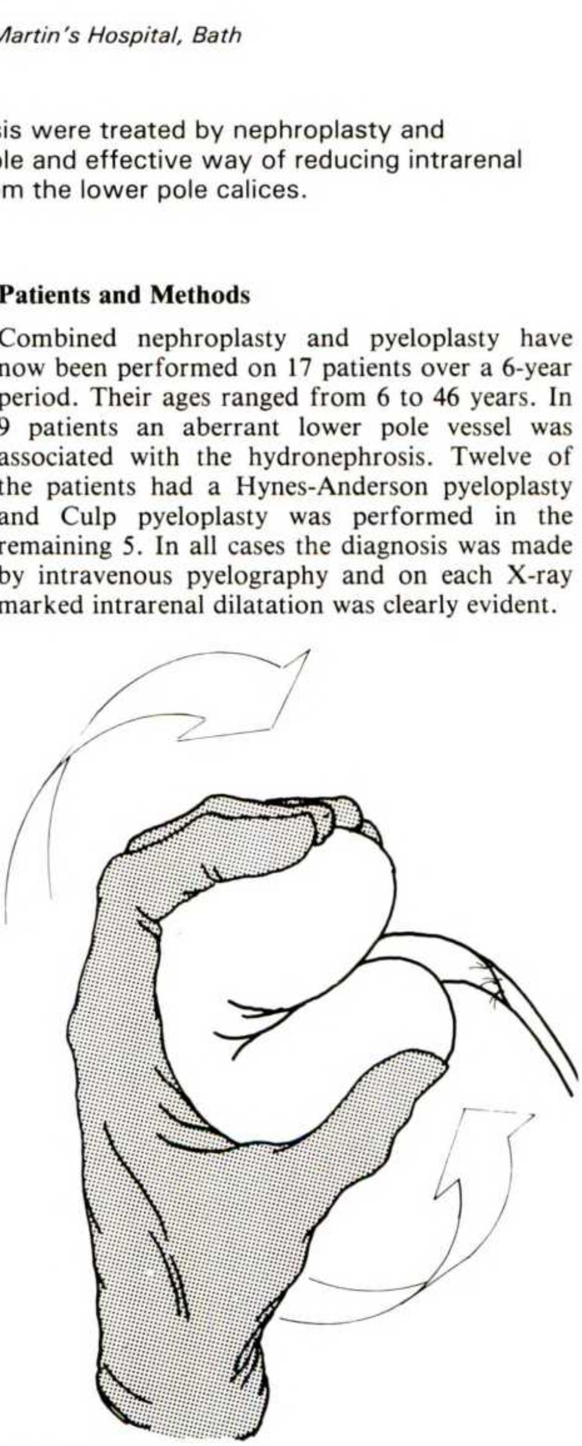

Fig. 1 Kidney folded.

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Operative Technique

The modified operative technique of this simple nephroplasty adds little time to a standard pyeloplasty procedure. At the completion of the pyeloplasty, and where necessary after transposition of any lower pole vessels, the kidney is held firmly in the surgeon's hands so as to bring the upper and lower poles together (Fig. 1). The poles are then sutured together with 2/0 chromic catgut (Fig. 2). Concurrent scarification or elevation of a small area of renal capsule on the adjoining areas of upper and lower poles will improve the subsequent adhesions between these poles. It is possible to complement this simple fixation by stitching a ribbon of fascia lata around the equator of the kidney so as to embrace the kidney like a belt, the 2 ends being tied in the region of the renal pelvis (Fig. 3).

On returning the folded kidney to the loin it will be seen to adopt a vertical drainage position (Fig. 4).

Results

All 17 patients made an uneventful recovery following the combined procedures. There were no significant post-operative complications. All patients were relieved of their presenting symptoms. In no case was it necessary to re-explore the kidney and no secondary nephrectomy procedures were required. It should be remembered that these were all severely obstructed kidneys with marked intrarenal dilatation. There has been no short-term incidence of hypertension in this group. Other studies have shown no increase in the incidence of hypertension over longer periods following nephroplasty (Stewart, 1957; Collins *et al.*, 1967; Smith, 1972).

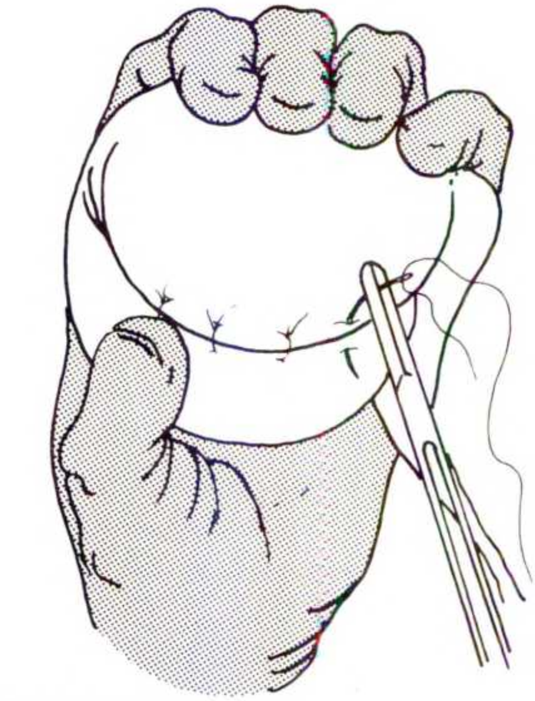

Fig. 2 Poles sutured.

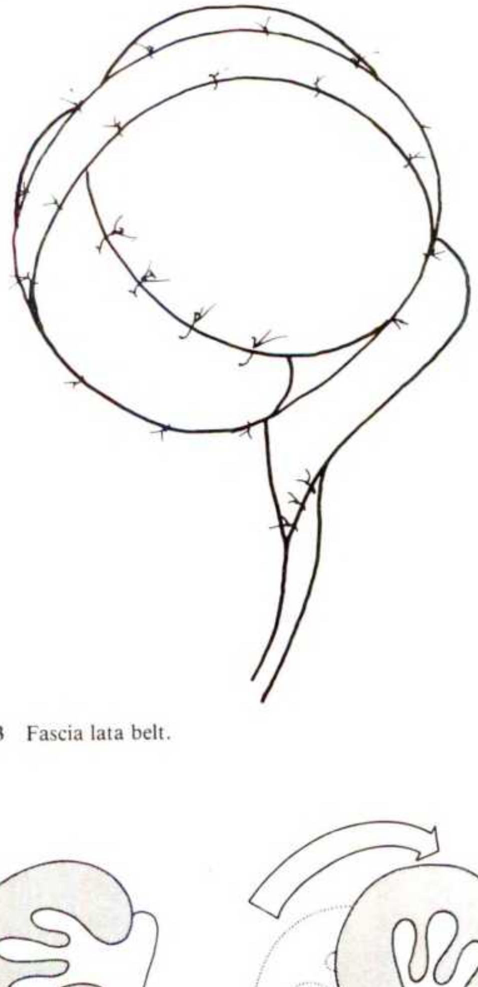

Fig. 3 Fascia lata belt.

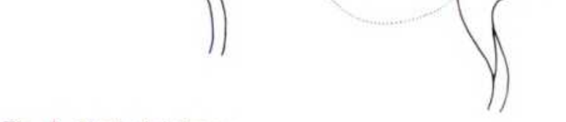

Fig. 4 Vertical drainage.

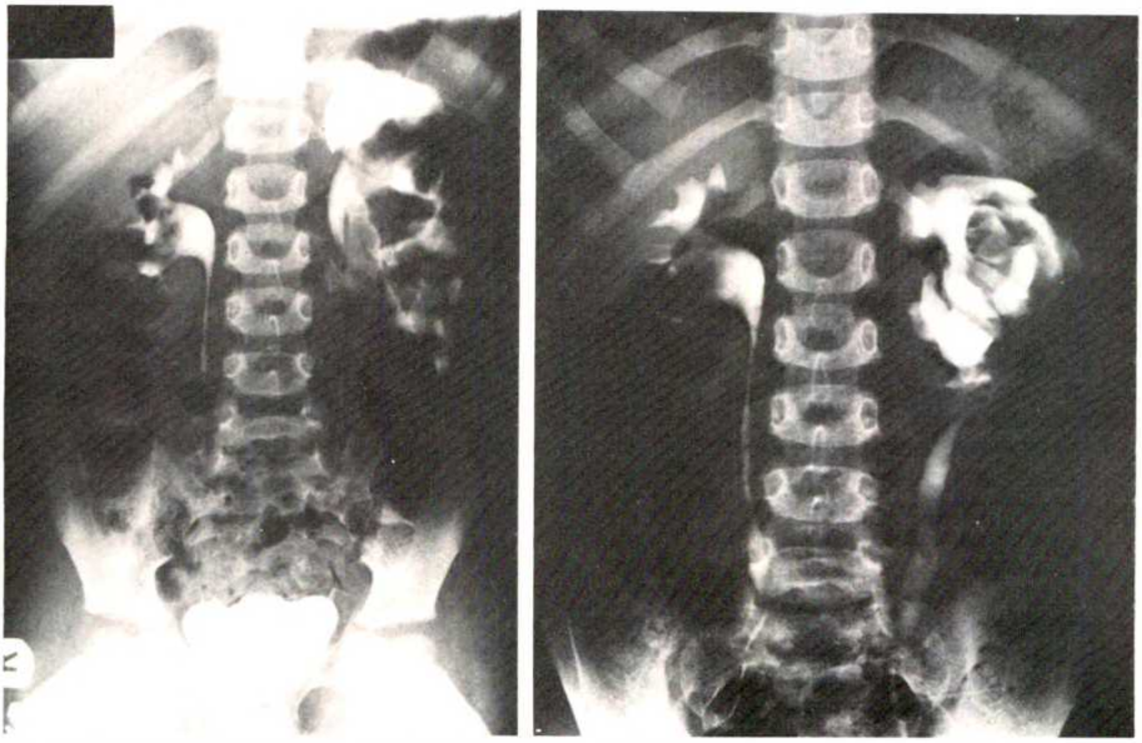

Fig. 5 (a) Pre-operative view of gross hydronephrosis with elongated "floppy" kidney and marked intrarenal dilatation. (b) Post-pyeloplasty and nephroplasty view of same kidney, showing compression of intrarenal dilatation and dependent drainage.

Discussion

Any pyeloplasty procedure aims to reduce the dilatation of the pelvicaliceal system by excision of redundant pelvis and to encourage drainage by reconstruction of the pelviureteric junction. These conditions are difficult to achieve when there is marked intrarenal dilatation. In this situation adequate excision is clearly impossible as a way of reducing dilatation. Also in these cases the lower pole calix will lie below the reconstructed pelviureteric junction and in the upright position may be difficult to drain. The consequence of leaving this residual space may be urinary stasis and secondary sepsis. Nephroplasty, by compressing the intrarenal space and elevating the lower pole calix, will reduce the risk of such stasis and sepsis. There is, unfortunately, no way in which it is possible to quantify the results of combined nephroplasty and pyeloplasty and hence it is impossible to demonstrate any significant improvement in results by the addition of nephroplasty in these 17 patients. However, all 17 had no problems with secondary sepsis and none required a secondary nephrectomy. It should be stressed again that these were all patients with severely obstructed kidneys with marked hydrocalicosis, cortical thinning and the typical elongated floppy appearance of the kidney as seen at operation and on the pre-operative intravenous pyelogram. The importance of kidney conservation in the management of hydronephrosis is well established. The addition of nephroplasty to a standard pyeloplasty operation requires little extra time and carries no specific complications. It will encourage the surgeon to persist in a conservative approach even when faced with a severely obstructed kidney.

It is concluded that nephroplasty in combination with pyeloplasty is a simple and effective way of reducing intrarenal dilatation and encouraging dependent drainage from the lower pole calices.

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Family History of Renal Stones in a Population Study of Stone-formers and Healthy Subjects

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Summary—Information on the family history of renal stone disease was obtained from over 2500 middle-aged men in a general health survey. A family history of stones was significantly more common among the stone-formers than among the controls, largely due to an increased frequency of stones among the fathers and brothers of the propositi.

This study thus supports previous suggestions that genetic factors play a part in the predisposition to stone formation. An increased tendency was also noted, however, among the wives of those whose relatives had stones, which suggests that environmental factors are involved.

Subjects with a family history of renal stones did not exhibit any particular characteristics in their laboratory profiles, but they appeared to be more prone to develop early and frequent recurrences.

Recent epidemiological studies indicate that renal stone disease is a rapidly increasing problem, already affecting more than 10% of the adult male population (Ljunghall, 1977). Several theories have been postulated for the formation and growth of renal stones but whatever the mechanisms may be which cause the actual crystallisation of salts in the urinary tract, it is likely that both environmental and genetic factors are involved. Thus stone disease appears to be increasing as standards of living rise in the industrialised world, but there are considerable geographical variations (Andersen, 1969; Ljunghall, 1978). Comparatively little attention has been paid to familial factors in the occurrence of urinary calculi, although it has been suggested that a polygenic form of inheritance accounts for part of the stone-forming propensity in some patients with calcium stones (McGeown, 1960; Resnick *et al.*, 1968). One problem encountered in genetic studies is the selection of valid patient and control materials, since adequate matching with regard to age, sex and socio-economic factors is essential. Thus patients from specialised stone clinics may not be typical of common stone-formers.

In this study a group of unselected stone-formers, detected in a general health survey, was investigated with regard to the family history of stone disease and compared with a control group of individuals from the same survey. In addition, serum and urinary electrolytes were determined in an attempt to detect factors involved in the stone-forming diathesis.

Material and Methods

Two general health surveys, primarily focused on the detection of cardiovascular risk factors, were carried out in the city of Uppsala between 1970 and 1975. All males born in 1915 and between 1920 and 1924 were invited to participate and 2653 men were examined, a participation rate of 83.2% (Ljunghall and Hedstrand, 1975; Ljunghall and Waern, 1977). These investigations included a detailed self-administered questionnaire containing a query on the previous history of renal stones. All patients who answered in the affirmative were recalled for interview. Information on the occurrence of renal stone disease among first-degree relatives was obtained through a postal questionnaire sent to all of the stone-formers. The same questionnaire was also sent to a control group consisting of 635 men born in 1915 and 1924 and reported to be stone-free at the survey. This enquiry was answered by 97.6% of the stone-formers and 96.4% of the control group.

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A family history of stones was considered to exist if at least one first-degree relative had experienced renal stones, even if the informant did not possess information concerning all of his relatives. On the other hand, the absence of a family history was accepted only if the informant could deny the occurrence of stones in all first-degree relatives. Those who did not possess full information in this respect were not included in the analysis of the family history. Adequate information, *i.e.* either a positive or a negative history, was obtained from 82.2% of the stone-formers and from 83.1% of the controls. The accuracy of the information was checked by scrutiny of hospital and out-patient records and by re-evaluation of X-ray films. In only 5 cases was the patient's history of stones found to be incorrect. The analysis of hospital discharge statistics and records did not reveal any further cases of stone disease not already detected by the screening methods described. Serum electrolytes and uric acid were determined in all cases and urinary electrolyte excretion was investigated in all subjects born in 1915 (Ljunghall and Waern, 1977).

Conventional statistical methods were used to calculate mean values and SD. Significances of differences between mean values were estimated by Student's t-test (2-tailed test). The χ^2-test (for small populations with Yates's correction) was used for comparison of frequencies. The accepted level of significance was $P<0.05$.

Results

Three hundred and seventy-eight individuals (14.2%) participating in the health surveys had a history of renal stones. A family history of stones, *i.e.* stones in at least one first-degree relative, was significantly more common among the stone-formers (29.6%) than among the stone-free subjects (17.4%) (Table 1).

Table 1 Number of Participants in the Study, Frequency of Stone Disease and Family History of Stones

No. of participants	*Frequency of stones*	*Family history of stones*	
		Stone-formers	*Stone-free controls*
2.653	14.2%	29.6%*	17.4%

* $P<0.001$, compared to controls.

Table 2 Frequency of Renal Stone Disease Among First-degree Relatives of Stone-forming and Non-stone-forming Middle-aged Men From a General Health Survey

	Frequency of stones (%)		*Significance of difference*
	Stone-formers	*Controls*	
Fathers	9.0	3.5	$P<0.01$
Mothers	3.1	1.7	NS
Brothers	14.2	5.2	$P<0.01$
Sisters	2.2	2.1	NS
Children	6.1	3.7	NS

Further analysis disclosed that there was a tendency towards an increased frequency among all first-degree relatives of the stone patients. This was most evident amongst the fathers and brothers, who had a significantly higher frequency of stones compared with the relatives of non-stone-forming subjects (Table 2).

Wives of the stone-formers were not more affected by stones than were the spouses of those in the control group. However, in families where the husband's relatives had a history of renal stones, the wives also had a significantly higher frequency of renal stone disease. A similar pattern was also observed for the control group (Table 3).

When stone-formers with a family history of stones were compared with those without any affected relatives an increased frequency of recurrences was noted, especially early and multiple recurrences (Table 4).

Stone-formers with a family history of stones did not display any differences in the laboratory profile, including serum and urinary electrolyes, compared with the other stone-formers, nor were there any differences in these respects within the control group (Table 5).

Table 3 Frequency of Renal Stone Disease Among the Wives of Stone-formers and Non-stone-forming Individuals Separated With Regard to the Husband's Family History of Stones

	Frequency of stone disease (%)		*Significance of difference*
	Family history of stones	*No family history*	
Wives of stone-formers	10.8	2.9	$P<0.01$
Wives of control subjects	7.0	3.8	$P<0.05$
All wives	8.8	3.5	$P<0.01$

Table 4 Age at Onset of Stone Disease, Total Recurrence Rate and the Frequency of Early and Multiple Recurrences in Male Stone-formers Separated With Regard to Family History of Stones

	Family history (n = 92)	*No family history (n = 219)*	*Significance of difference*
Age at onset (years)	39.2	38.9	NS
Total recurrence rate (%)	50.0	40.2	NS
Recurrence in 5 years (%)	47.8	25.1	$P<0.001$
Recurrence in 10 years (%)	57.6	31.5	$P<0.001$
More than 3 recurrences (%)	24.0	13.2	$P<0.05$

Discussion

The present study shows that a family history of stones is more common among stone-formers than among non-stone-forming individuals. Several rare metabolic disorders such as cystinuria, xanthinuria and primary hyperoxaluria are known to be hereditary, but they account for only a small part of all stone formation. The present findings suggest that genetic factors are involved in common renal stone disease in unselected stone-formers.

Resnick *et al.* (1968) found evidence to support the hypothesis that the tendency to form calcium oxalate stones is regulated by a polygenic system. Our results support this concept, as does our previous study of the HLA system among recurrent renal stone-formers, which showed an increased frequency of the antigen B27, possibly of importance in the pathogenesis of hypercalciuria (Säfwenberg *et al.*, 1978).

However, first-degree relatives not only share some genetic information but are also exposed, at least in part, to the same environment and often develop similar patterns of living. To evaluate the possible importance of the common environment the occurrence of stones was analysed among the wives of both the stone-formers and the control subjects. The finding of a higher incidence of stones among the females in those families with a history of stones among their relatives indicates that environmental factors may also be involved. The importance of non-genetic household factors in stone disease was stressed by White *et al.* (1969) from their findings of an increased urinary excretion of calcium in the spouses of stone-formers when compared to those of stone-free subjects.

In the present study an unselected group of stone-formers was examined without regard to current stone formation. From an epidemiological point of view the advantages of such an experimental design are obvious, as this group of patients should be representative of common renal stone-formers in the population and the control groups could be closely matched for age and sex.

These advantages, however, were gained possibly at the expense of accuracy of diagnosis and

Table 5 Serum and Urinary Electrolytes in Stone-formers and Controls From a General Health Survey Separated With Regard to Family History of Renal Stone Disease (Mean values ±SD)

	Stone-formers		*Controls*	
	Family history	*No family history*	*Family history*	*No family history*
Serum electrolytes (mmol/l)				
Calcium	2.44±0.05	2.41±0.07	2.40±0.08	2.41±0.08
Phosphate	0.93±0.14	0.91±0.11	0.90±0.14	0.95±0.28
Uric acid	0.25±0.04	0.26±0.06	0.29±0.08	0.27±0.07
Urinary electrolytes (mmol/24 h)				
Calcium	6.85±3.07	6.85±4.25	4.85±3.25	5.33±2.28
Magnesium	3.83±1.21	3.85±1.42	3.90±2.08	3.80±1.59
Sodium	153.00±65.00	162.00±79.00	154.00±54.00	155.00±60.00
Potassium	75.00±33.00	70.00±21.00	73.00±22.00	70.00±24.00
Phosphate	32.00±5.00	31.00±7.00	30.00±7.00	29.00±8.00

completeness of information. Previous studies have indicated that the informant's knowledge of his own stone disease was almost always accurate (Ljunghall, 1977) and this is probably also true of reported cases of stones in his family. On the other hand, it is possible that bias may arise from the fact that stone-formers have an increased interest in stones among their relatives and stone-free subjects may underestimate stone disease in their first-degree relatives. Although ideally an extended survey should obtain firsthand information from all members of the families, it appears from earlier studies that such a bias was not strong enough to have a significant effect on the results (McGeown, 1960; Resnick *et al.*, 1968).

Several theories have been put forward to explain stone formation and growth; current opinion on the physicochemical background of stone formation implies a disturbance of the balance between the supersaturating and the inhibitory factors (Robertson *et al.*, 1976).

In previous attempts to identify the factor responsible for the familial predisposition to stone formation, most attention has been directed to calcium metabolism and it has been suggested that hypercalciuria (presumably caused by an increased dietary intake of calcium) is the connecting link (White *et al.*, 1969; Transböl and Frydendal, 1973). None of these investigations, however, studied the calcium intake or the incidence of stones among the relatives of stone patients.

We have earlier demonstrated that stone-formers, when compared to matched controls, do not have an increased intake of calcium or vitamin D (Ljunghall and Hedstrand, 1976) and in the present study there were no differences in the serum or urinary calcium between stone patients and the control group when separated with regard to the family history of stones. Although hypercalciuria is commonly found among recurrent stone-formers, as in the present study, it seems unlikely that the familial diathesis for stone formation is mediated primarily through a raised urinary calcium.

Whatever the biochemical cause for the increased frequency of stone formation in these families may be, it appeared that this group of patients had clinical characteristics in common with a high recurrence rate, particularly early and multiple recurrences. Detailed metabolic investigations have failed to disclose patients with an increased tendency to stone formation (Powis *et al.*, 1974). This study suggests that patients with a family history of stone disease should be regarded as being at risk. Early clinical and metabolic evaluation is worthwhile and attempts at prevention of stone formation are justified early in the course of the disease.

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Urinary Inhibitors of the Formation of Calcium Oxalate

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Summary—Normal urine was examined for substances which inhibited the formation of calcium oxalate, using a separation scheme which involved ultrafiltration, alcohol precipitation, electrophoresis and paper chromatography. The major anionic inhibitors were found to be citric acid, isocitric acid and pyrophosphate.

The inhibitory activity of urine and that of an artificial urine having the same concentration of urea, creatinine, sodium, potassium, magnesium, calcium, ammonia, sulphate, chloride, inorganic phosphate, oxalate, citrate, isocitrate and pyrophosphate, and the same pH were identical. This confirmed that urine does not contain an unidentified potent substance which inhibits the formation of calcium oxalate.

It has long been recognised that urine contains substances which inhibit the formation of calcium oxalate and calcium phosphate, the compounds most frequently found in upper urinary tract stones (Sutor *et al.*, 1974). The well-known ones are citric acid and pyrophosphate, but it has been claimed that potent unidentified inhibitors are also present and the references in the literature are numerous.

In order to establish whether such compounds do exist, we have subjected urine from normal subjects to several isolation procedures (ultrafiltration, alcohol precipitation, electrophoresis and paper chromatography). As a result of these steps, substances which affect the nucleation and crystal growth of calcium phosphate were isolated and identified, but no previously unknown inhibitor was found (Sutor *et al.*, 1978a). Subsequently we have shown that urine and an artificial urine containing the same concentration of urea, creatinine, sodium, potassium, magnesium, calcium, ammonia, sulphate, chloride, inorganic phosphate, citrate, isocitrate and pyrophosphate, and having the same pH, have the same inhibitory activity in the calcium-phosphate assay system (Sutor *et al.*, 1978b).

We now report a similar study of substances which inhibit the nucleation and crystal growth of calcium oxalate as followed by a precipitation reaction in which the amount of calcium oxalate formed after a certain time is determined.

Materials and Methods

Analytical grade reagents, when available, and deionised water were used throughout.

Assay Method

The presence or absence of material which inhibited the formation of calcium oxalate was determined by a nephelometric procedure (Sutor, 1976). Calcium oxalate was formed by adding sodium oxalate solution (5 mmol/l) to an equal volume of calcium chloride dihydrate solution (5 mmol/l) which had been mixed with the test or control solution, and the turbidity of the solution was measured at one-minute intervals for 10 min. Depending on the amount of material available, the system consisted of either 2½ ml of each reagent and 5 ml of test solution when this was concentrated (method 1) or 1 ml of each reagent and 8 ml of test solution when this was dilute (method 2). The technique gives an indirect estimate of the amount of material formed at a particular time.

In both methods allowance must be made for the effect of ionic strength and pH on the solubility of calcium oxalate. In the latter case the pH of tests to be compared was adjusted to the same value within the range 5.6 to 7.0. In the former the concentration of added electrolyte, and hence

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the ionic strength of the solution in which the solubility of calcium oxalate was increased, was determined using sodium chloride. The ionic strength of material obtained at each purification step was not known. As this material was usually acidic, the amount of sodium in the sodium hydroxide required to neutralise it was compared with the amount of sodium in the added sodium chloride which caused interference in the test system. If the former was greater than the latter, the solution was diluted so that the volume added to the test system contained less sodium than that at which interference occurred.

The method was reproducible and showed little variation with small changes in room temperature. However, when quantitative measurements were necessary, as in the comparison of the inhibitory activity of normal and artificial urines, all the solutions and, between measurements, the test tube containing the assay, were kept in a constant temperature bath at 25°C. The drop in temperature of the assay when the test tube was transferred to the nephelometer head was not more than 0.5°C.

About 2 to 3 ml of normal urine in method 1 were sufficient to reduce the amount of calcium oxalate formed after the reaction had proceeded for 10 min at room temperature or at 25°C. Similar volumes were used to test the activity of material obtained from ultrafiltration and alcohol precipitation. When extracts of urine from electrophoresis and paper chromatography were tested, all of the material in each extract was rotary evaporated to give enough for only 2 tests, generally using method 2. The actual amount included in the test was subject to the restrictions on the ionic strength given above. In this way small amounts of inhibitors were not missed.

Urine Samples

The urine from 2 healthy adults with no history of urinary stones was subjected to all of the isolation steps described. Urine from one normal male was also subjected to some of these steps. In all cases the active material behaved comparably. Invariably the urine was the early morning sample. The person emptied his/her bladder before going to bed and passed the specimen in the morning before breakfast was eaten. No preservative was added and processing was started within 2 h of the sample being voided.

For comparison of inhibitory activity of normal and artificial urine, early morning urine samples were obtained from 10 healthy adults with no history of urinary tract disease. The age range of these normal subjects was 25 to 62 years and there were 3 females and 7 males. A preservative was not added as it could introduce artefacts.

Isolation and Identification of Inhibitors

The urine samples were treated in the same way as for the isolation and identification of substances which inhibit the crystal growth of calcium phosphate (Sutor *et al.*, 1978a). The steps involved were ultrafiltration, alcohol precipitation, electrophoresis and paper chromatography.

Comparison of the Activity of Normal and Artificial Urine

The urine was immediately filtered as for calcium phosphate (Sutor *et al.*, 1978b). Again it was found expedient to dilute the filtered urine with water in the ratio 3:1, to minimise the chances of precipitation occurring. The activity of the urine was determined using the nephelometric procedure and the reading at 10 min was compared with that for a control run using water.

The concentration in the urine or diluted urine of sodium, potassium, calcium, magnesium, ammonia, chloride, phosphate, sulphate, creatinine, urea, citric acid, isocitric acid and pyrophosphate were determined as described by Sutor *et al.* (1978b). Oxalate was measured by an enzyme method (Hallson and Rose, 1974).

An artificial urine was prepared having the same concentration of the above compounds and ions and the same pH as the original urine or dilute urine (Sutor *et al.*, 1978b). The artificial urine was tested in the assay system and the results compared with control runs using water.

Results

Isolation and Identification of Inhibitors

The systematic breakdown of urine using the different techniques mentioned yielded anionic substances which inhibited the formation of calcium oxalate. These were citric acid, isocitric acid and pyrophosphate.

Comparison of the Activity of Normal and Artificial Urine

Agreement between duplicate runs in the assay system was usually good, each value being within ±6% of the mean.

Table Values of the Ratio (Turbidity in Test/Turbidity in Control) in the Calcium Oxalate Assay System After the Reaction had Proceeded for 10 min. The Turbidities are the Mean Values of 2 Concordant Runs

Ratio		*Volume (ml) of urine in test*
Urine	*Artificial urine*	
0.56	0.53	3
0.29	0.29	3
0.47	0.52	3
0.47	0.51	2
0.97	0.97	3
0.89	0.88	3½*
1.13	1.13	3½*
0.73	0.79	3*
0.76	0.79	3*
0.72	0.71	3*

* Urine diluted with water in the ratio 3 : 1.

Comparison of the ratios (turbidity reading in test/turbidity reading in control) after the reaction had proceeded for 10 min showed that these were almost identical for urine and its corresponding artificial urine (Table).

Discussion

Fractionation of urine suggested, and quantitative measurements on the activity of urine and artificial urine confirmed, that the normal urines tested did not contain a potent unidentified substance which inhibited the formation of calcium oxalate. The assay method is not as sensitive as that used for identifying substances which inhibit the formation of calcium phosphate, but compounds of comparable potency to that of citric acid, isocitric acid and pyrophosphate would have been detected (Sutor, 1976; Sutor and Percival, 1978).

All urines except one inhibited the amount of calcium oxalate formed in our assay system. The exception was one with a high calcium concentration of 10.5 mmol/l. The inhibitory activity resulted from the net effect of the action of most of the substances in the artificial urine on the formation of calcium oxalate. Calcium and oxalate accelerate the reaction and increase the amount of material produced, whereas the other ions contribute to the ionic strength and so increase the solubility of calcium oxalate. This slows down the reaction and decreases the amount of calcium oxalate produced. Citric acid and isocitric acid form stable complexes with calcium and thus reduce the rate of formation of calcium oxalate. Pyrophosphate is adsorbed on to crystal faces and inhibits further deposition on them. Urea and creatinine were included because they are basic urinary constituents.

The acid mucopolysaccharide which inhibits the agglomeration of calcium oxalate monohydrate (Robertson *et al.*, 1973) made no contribution to the activity of the urine in this assay system, and therefore has little effect on the amount of calcium oxalate produced.

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The Modified Lumbotomy Versus the Oblique Loin Incision for Renal Surgery

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Summary—The time to full mobility and total analgesic requirements have been assessed in 40 patients undergoing renal surgery by the oblique loin incision or the posterior lumbotomy approach. By these criteria the lumbotomy group fared better than patients who had oblique incisions. We consider lumbotomy to be a valuable incision which should be in the repertoire of every urologist.

In 1869 Gustav Simon (Murphy, 1972) performed the first elective nephrectomy using a vertical retroperitoneal muscle-splitting incision. This was followed in 1880 by Henry Morris's first nephrolithotomy (Murphy, 1972) through an oblique retroperitoneal muscle-cutting incision. The aim of our trial was to show whether a modification of Simon's original muscle-splitting lumbotomy incision decreased post-operative pain, length of stay in hospital and post-operative immobility compared with Morris's muscle-cutting type of incision.

Patients and Methods

Two groups of patients were studied. Twenty patients had a modified lumbotomy incision (Fig. 1). The other 20 had an oblique incision (Fig. 2).

We have modified the lumbotomy approach (Wickham, 1977) so that the skin incision is made obliquely to follow Langer's lines, as we had previously found that the lower end of the classical vertical incision tended to hyperplastic scar formation and became unsightly. The incision commences superiorly over the posterior angle of the twelfth rib and extends downwards and forwards for about 10 cm to finish just above the iliac crest near the anterior superior iliac spine. The underlying fat is divided, exposing the lateral portion of latissimus dorsi muscle which is divided in the line of its fibres to reveal the erector spinae muscle mass and the lumbar fascia arising from its lateral border. The lumbar fascia is divided longitudinally and parallel close to the lateral edge of the erector spinae sheath to disclose the quadratus lumborum posteriorly and the perinephric fat anteriorly. Should further exposure be required superiorly, excision of one-inch portions of the posterior ends of the twelfth (and occasionally the eleventh and tenth) ribs may be performed.

Patients were allocated to one or other group depending upon the operation to be performed and the preference of the surgeon. Eight surgeons were involved. Patients requiring more extensive incisions and those who had had previous surgery on the same side were excluded. The following factors were assessed.

Degree of Mobilisation

Using a simple scoring chart graded 1 to 4, the degree of mobility of the patient on each post-operative day was assessed by an independent senior member of the nursing staff.

Analgesia

The total number of major analgesic injections (Omnopon) required was recorded. The number of minor analgesic doses (Distalgesic) administered was also recorded, from operation to the end of 1 day of full mobility, and from operation to the end of 3 days of full mobility. All patients stayed in hospital up to this stage in their recovery, allowing their analgesic requirements to be accurately compared.

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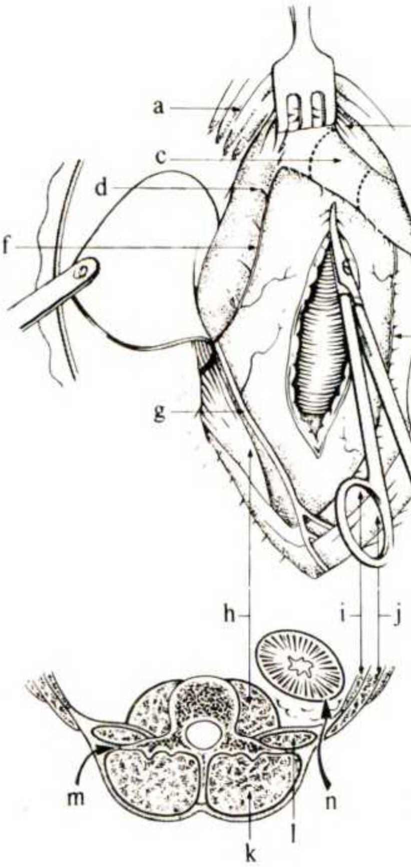
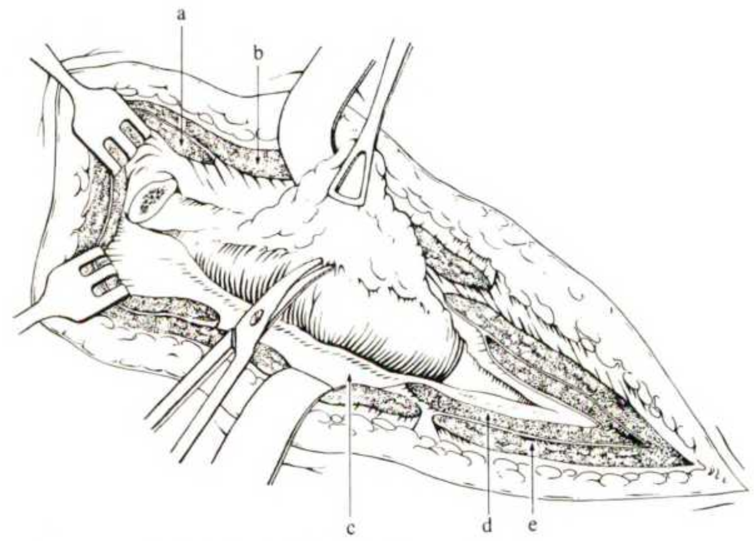


a) **Latissimus dorsi**
b) Serratus posterior inferior
c) 12th rib
d) Erector spinae
e) Subcostal nerve
f) Cut edge of lumbar fascia
g) Iliohypogastric nerve
h) **Psoas muscle**
i) Transversus abdominis
j) Internal oblique
k) Paraspinal muscle mass
l) Quadratus lumborum
m) Route to avoid
n) Approach through lumbar fascia

Fig. 1



a) Serratus posterior inferior
b) Latissimus dorsi
c) Transversus abdominis
d) Internal oblique
e) External oblique

Fig. 2

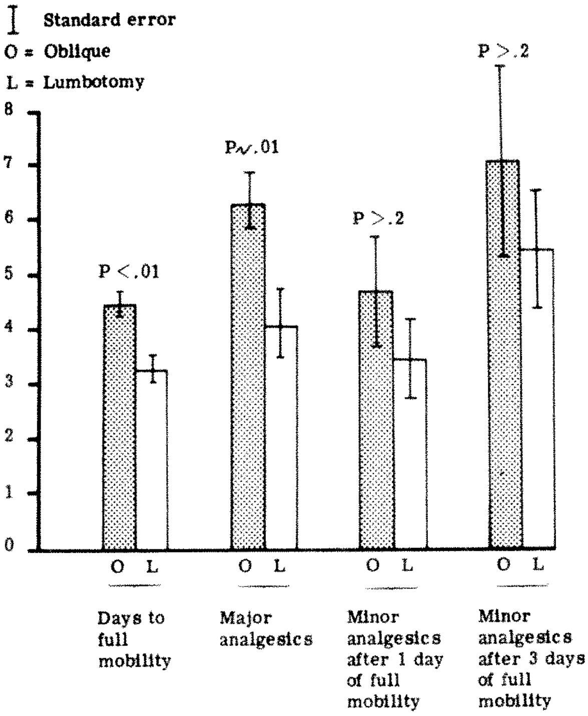


Fig. 3

Time in Hospital

The time in hospital from operation to discharge was recorded.

Intravenous Fluid

The time for which patients required intravenous fluid was charted.

Results

For each criterion considered, lumbotomy patients fared better than their oblique counterparts.

Mobility

All patients having achieved full mobility maintained this status. There was a significant difference between groups. The number of days to full mobility in patients who underwent an oblique incision was 4.3 (±SD 1.1) and the number of days to full mobility in the lumbotomy group was 3.3 (±SD 1.1) (by using "t" test, $P<0.01$).

Major Analgesics

Lumbotomy patients required 4.2 (±SD 2.8) major analgesic injections and patients who had oblique incisions required 6.3 (±SD 2.1) injections (by "t" test, $P<0.02$).

Minor Analgesics

Up to and including one day of full mobility, oblique incision patients averaged 4.8 (±SD 4.5) and lumbotomies averaged 3.5 (±SD 3.2) doses of Distalgesic.

Up to and including 3 days of full mobility, obliques averaged 7.8 (±SD 6.2) and lumbotomies 5.5 (±SD 4.6) doses of minor analgesics.

These differences did not reach statistical significance.

Time in Hospital

The mean time in hospital for lumbotomy patients was 9.0 days compared with 11.2 days for oblique incision patients.

Time on Intravenous Infusion

Following lumbotomy, patients averaged 41.7 h of intravenous infusion. Oblique incision patients averaged 67.2 h.

Discussion

The advantage of the muscle-splitting lumbotomy approach is that it disrupts less tissue than the more anterior muscle-cutting oblique incision, and by avoiding nerve damage it prevents subsequent muscular atrophy, abdominal wall weakness, paraesthesia and painful hyperaesthesia (Harbison, 1974; Ward *et al.*, 1976).

Statistical analysis confirms that the lumbotomy incision allows significantly quicker mobilisation and produces a significant reduction in the number of major analgesic injections required.

The number of doses of minor analgesics is a less reliable index of post-operative pain than the number of major analgesic injections administered, as minor analgesics tend to be more readily available, dispensed with less discretion and may be given for general discomfort as well as for pain due to operation. The fact that the difference in minor analgesic requirements between the 2 groups was not significant is therefore of less relevance.

Duration of stay in hospital following operation was intended as an indicator of disability following surgery, but it was found that many other factors influenced this. The time taken to reach full mobility was considered a better indicator of this.

The period for which patients required intravenous fluids was charted as it was hoped that this would indicate the length of post-operative ileus. Infusions were maintained for varying times, however, depending on the whims of staff and the need for concomitant parenteral therapy.

In our experience, lumbotomy is the ideal incision for upper ureteric surgery and for procedures on the renal pelvis and major collecting system when the kidney does not require full mobilisation. Lumbotomy may also be used with discretion for more extensive renal procedures when full mobilisation is required. With increasing experience, indications for this approach will become more numerous. However, enthusiasm may need to be tempered by the nature of the lesion and the experience of the surgeon. Lumbotomy may cause the operation to be a little more difficult for the urologist but it does make recovery easier for the patient.

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Benign Tumours Developing at the Site of Ureterosigmoidostomy

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Summary—Two cases of benign tumours complicating ureterosigmoidostomy are described. The latent period between diversion and the development of tumour is long and careful follow-up of patients with ureterosigmoidostomy is recommended. It would seem highly probable that adenomatous polyps developing at the site of anastomosis may, if undetected, undergo malignant change to adenocarcinoma.

All of the tumours recorded following ureterosigmoid diversion have been associated with a nipple type ureterocolic anastomosis and mucosa-to-mucosa anastomosis may possibly prevent this complication.

Ureterosigmoidostomy was first described by Simon in 1852. Tumour formation at the site of the anastomosis is a rare complication and was first described by Hammer in 1929. Since that time a further 22 cases of malignant tumour have been recorded in the world literature (Mogg, 1977) but only 8 cases of benign tumour complicating ureterosigmoidostomy have been reported. This paper reviews the literature and presents 2 further cases of benign tumour occurring at the site of ureterosigmoidostomy.

Case Reports

Case 1

E.C., born in 1963 with ectopia vesicae. Treated by ureterosigmoidostomy using a Coffey I technique in the same year. She remained well for 13 years but then presented with an episode of left loin pain, moderately raised blood urea and hypchloraemic acidosis. Investigations confirmed a poorly functioning left kidney (Fig. 1) shown by antegrade pyelogram to be caused by an obstruction at the site of the ureterosigmoidostomy (Fig. 2). Laparotomy revealed a mobile mass at the site of the left ureterosigmoid anastomosis. The tumour was excised and the ureter reimplanted. Histology of the tumour revealed the typical features of an adenomatous polyp (Fig. 3). Follow-up excretion urography showed a satisfactory return of function to the left kidney (Fig. 4).

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Case 2

S.F., a 20-year-old man born with ectopia vesicae. Treated at the age of 12 years by a Coffey I uretero-

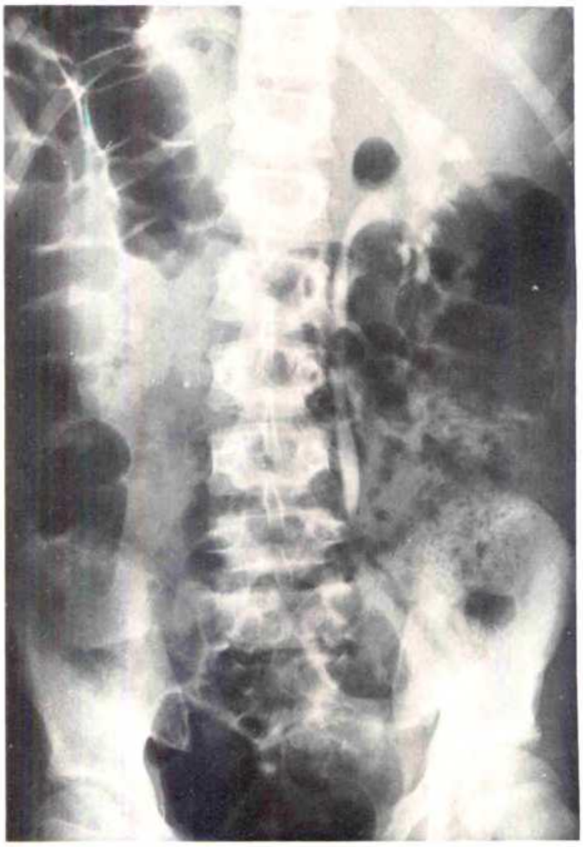

Fig. 1 Excretion urogram showing normal right kidney and poorly functioning left kidney.

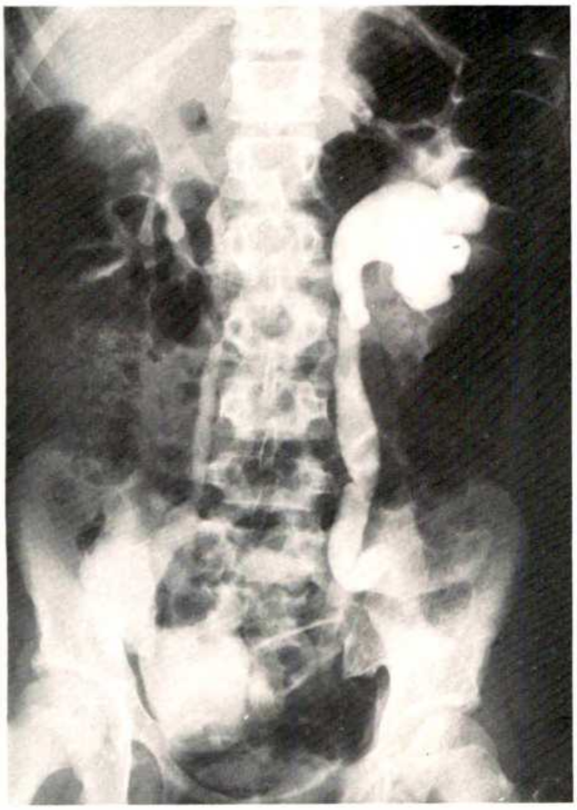

Fig. 2 Antegrade pyelogram confirming obstructed left kidney and ureter.

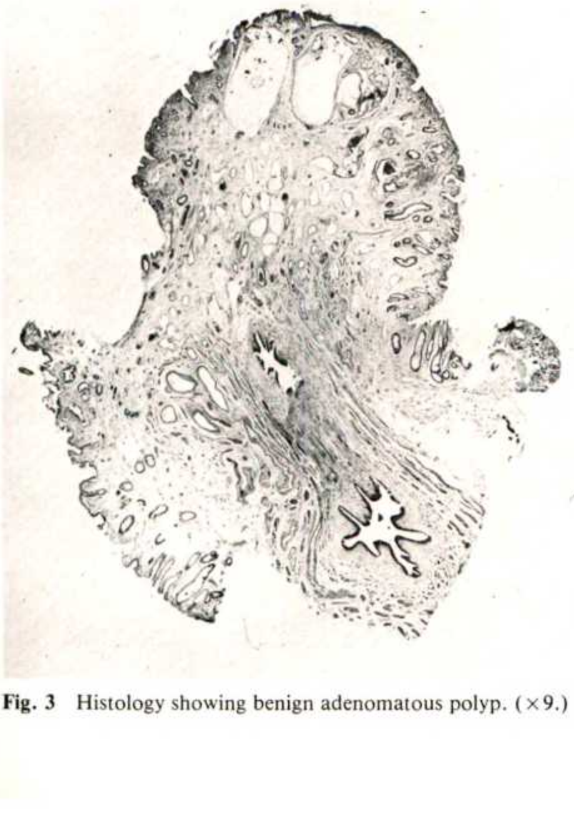

Fig. 3 Histology showing benign adenomatous polyp. (×9.)

sigmoidostomy. He remained well for 7 years but then presented with a history of severe right loin pain and rectal bleeding. Urography revealed gross ureteric obstruction (Fig. 5).

At laparotomy tumour masses at the site of both ureterosigmoidostomy anastomoses were excised. The ureters were then connected to an ileal conduit. Histology of the tumours revealed benign inflammatory polyps (Fig. 6). Follow-up at 12 months shows satisfactory function in the upper tracts with good drainage across the conduit (Fig. 7).

Discussion

The precise cause of tumours occurring at the site of ureterocolic anastomosis is not clear, though the close anatomical relationship between tumour and anastomotic site is unlikely to be fortuitous.

Repeated trauma to the projecting lower end of the ureter with alternating ulceration and mucosal repair leading to epithelial hyperplasia might sometimes be expected to induce a tumour (Gillman, 1964). In this respect it is worth noting that a nipple-type ureterocolic anastomosis was done on both of the patients described above.

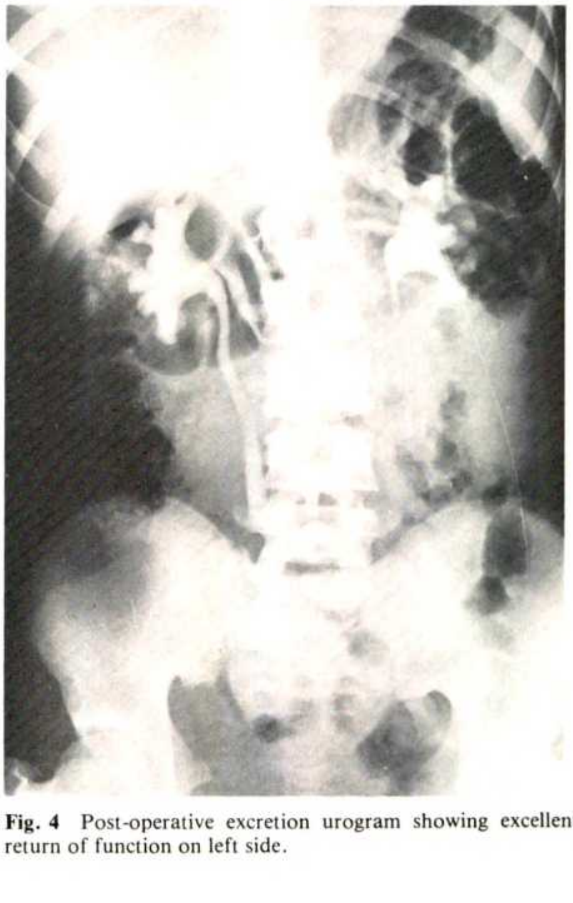

Fig. 4 Post-operative excretion urogram showing excellent return of function on left side.

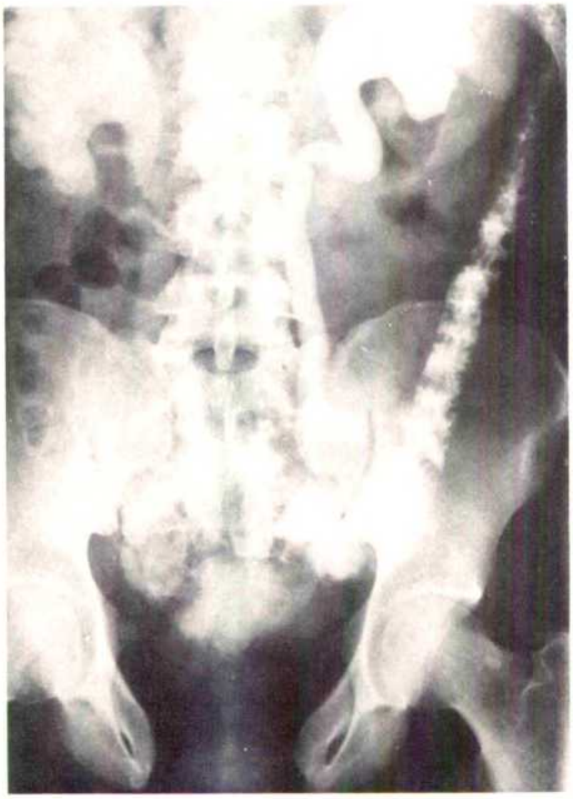

Fig. 5 Excretion urogram demonstrating gross bilateral ureteric obstruction.

Indeed, a review of the literature shows that all of the tumours described were related to such nipple-type anastomotic procedures.

The direct action of urine on the colonic mucosa may also be a factor in tumour formation but this does not explain all of the cases. In the case reported by Gillman (1964), for example, the colon was exposed to urine for only 1 year, yet a polyp developed at the site of the ureterocolic anastomosis 7 years later.

A review of 8 benign and 23 malignant tumours occurring at the site of ureterosigmoid anastomosis described in the world literature is shown in the table. The mean latent period between the development of tumour in patients diverted for malignant lesions was 6 years, whilst the mean latent period before the development of tumour in patients diverted for congenital lesions was 19 years. It is not clear why some patients in this

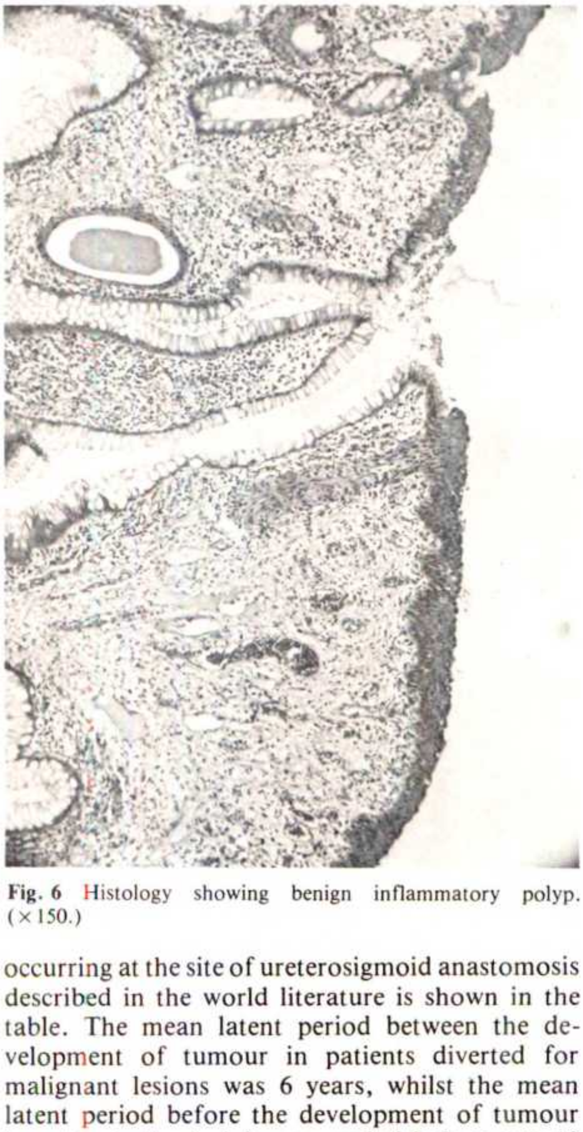

Fig. 6 Histology showing benign inflammatory polyp. (×150.)

Table Analysis of 31 Cases Recorded in the Literature up to 1977

Type of tumour	*Reason for ureterosigmoidostomy*		*Latent period from uretero-sigmoidostomy to development of tumour*	
	Benign	*Malignant*	*Benign*	*Malignant*
Adenomatous polyp 8	6	2	14-30 years	3-7 years
Adenocarcinoma 14	10	4*	17-34 years	6-8 years
Transitional cell carcinoma 3	1	2	17 years	1-4 years
Carcinoma of indeterminate type† 6	6	—	10-30 years	—

* 3 Transitional cell carcinoma of bladder, 1 Squamous cell carcinoma of bladder.

† 3 Anaplastic carcinoma, 2 Colloid carcinoma, 1 Scirrhous carcinoma.

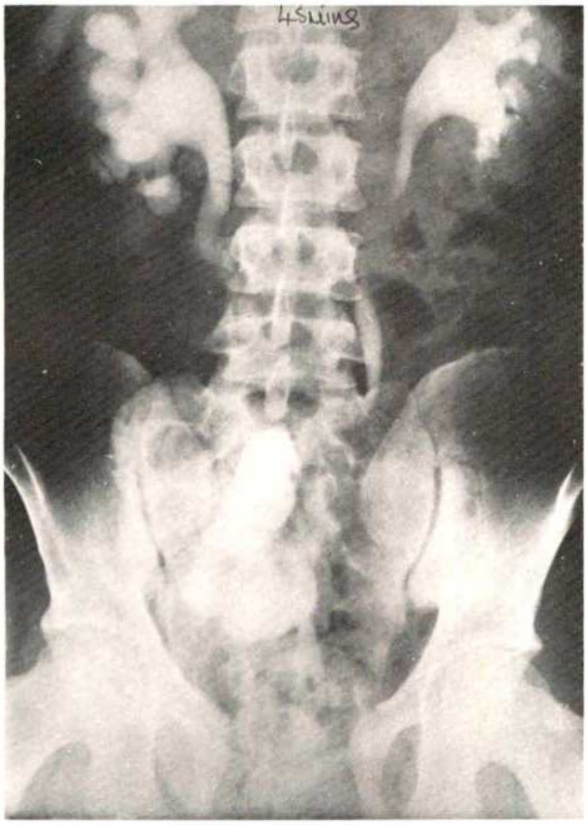

Fig. 7 Post-operative excretion urogram showing improvement with satisfactory conduit.

collected series developed adenomatous polyps and others adenocarcinoma. The mean latent period from diversion to diagnosis of adenomatous polyps was 17 years and 21 years from diversion to the development of adenocarcinoma. It is possible that the adenocarcinoma may develop as a result of malignant change in adenomatous polyps and there is evidence that such polyps are prone to undergo malignant change (Helwig, 1959; Morson, 1962).

Because of this long latent period between diversion and tumour diagnosis, attention should be paid to any symptoms referable to the bowel or urinary tract in patients who have undergone ureterosigmoidostomy. When such patients present, excretion urography and colonoscopy should be undertaken immediately. Biopsy is essential in assessing prognosis. Transitional cell and anaplastic tumours have a very poor prognosis, whilst it is more favourable with adenocarcinoma. The prognosis would seem to be even better with adenomatous polyps, as indeed is so far the case in both of the patients presented.

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Bladder Augmentation—a Long-Term Review

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Summary—Fifty-nine patients who had undergone augmentation cystoplasty were studied over a period of 18 years. The indications for the operation were a tuberculous contracted bladder in 51, interstitial cystitis in 7 and carcinoma in 1.

The ileum was used in one patient, the colon in 16 and the caecum in 42. The results did not seem to be influenced by the segment of bowel and the long-term results of using the colon as bladder substitute were similar to those achieved by using the caecum.

An excellent result has been achieved in 78% of the 49 surviving patients. Operative mortality was 5.1% (3 patients). Contraindications include progressive severe renal failure, enuresis and a history of previous psychiatric disturbance.

Tizzoni and Foggi (1888) were the first to report the operation of cystoplasty when they performed an ileocystoplasty on a dog, but it was not until 1899 that Von Mikulicz carried out the first ileocystoplasty on a man for a small contracted bladder. The colon was used for bladder augmentation by Lemoine (1913) and in 1923 Scheele published a monograph describing his results using the ileum in both the ring and the U-shaped form of ileocystoplasties. The results, however, were poor as at that time most of the cases of contracted bladder were caused by tuberculosis, a disease with a high mortality as antituberculous chemotherapeutic agents had not then been discovered.

Once the antibiotic era had begun many surgeons recommended using the intestine for bladder augmentation and replacement for the tuberculous contracted bladder, and later for interstitial cystitis, irradiation cystitis, neurogenic bladder, enuresis, chemical cystitis and bladder cancer, where pain, frequency of micturition and nocturia were the predominant symptoms.

The purpose of this study is to review 59 patients who have been treated by bladder augmentation, 51 because of tuberculosis, 7 for interstitial cystitis and 1 for carcinoma, to analyse the results, surgical management, indications and complications and to suggest an extension of this procedure for the treatment of carefully selected cases of bladder tumours.

Patients and Methods

Since 1959, 59 enterocystoplasties for bladder augmentation have been carried out. All of the patients, except one who returned to Spain, have been followed up and carefully assessed. Thirty-six were male and 23 female and the age distribution is shown in Table 1. The operative procedures were ileocystoplasty in 1, colocystoplasty in 16 and caecocystoplasty in 42.

The operative technique is not described in detail as we believe that this is a matter of individual choice; nevertheless, certain aspects are worth emphasising. Bowel preparation was commenced 48 h before surgery and originally consisted of 1 g oral streptomycin 8-hourly together with succinylsulphathiazole colonic washouts. This has recently been superseded by neomycin 1 g tds, metronidazole 200 mg tds, together with 500 ml of a solution of 5% aqueous povidone iodine given as a retention enema the evening prior to surgery. If the colon is used for augmentation a flap technique formed from at least 25 to 30 cm of sigmoid colon is recommended as it

Table 1

	Ages of patients	
	Colocystoplasty	*Caecocystoplasty*
10–20	1	2
21–30	4	8
31–40	4	16
41–50	6	8
51–60	1	5
61–70	0	4

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empties better and produces a more satisfactory pouch. If the caecum is selected the whole of the colon, including the hepatic flexure, should be mobilised as this not only facilitates the anastomosis between the ileum and the ascending colon, but also allows the mobility of the caecum to be assessed. Occasionally the caecal mesocolon is short and in these cases a little more length can be obtained by making incisions through the peritoneal surface of the mesocolon. The amount of ileum that is retained attached to the caecum is not important unless the ureters are being anastomosed into the ileum, in which case at least 25 cm of ileum should be available for the ureteroileal anastomosis. Whenever a ureteroileal anastomosis is indicated this part of the operation should be carried out before the caecum is sutured to the bladder; otherwise the technical difficulties may be insuperable.

The technique suggested for ureteric anastomosis is a reflux-preventing procedure provided that the ureters are not too rigid and fibrotic, as in our experience the nipple method has not prevented reflux when the ileocaecal valve is incompetent. If the ureters are rigid an end-to-end anastomosis is carried out and ureteric reflux accepted, but if they are dilated they can be tailored so that a reflux-preventing technique can be used. In those cases of resolving tuberculous cystitis, inflammation is not a contraindication to surgery, but as an extra precaution the omentum should be wrapped round the vesicocaecal anastomosis. It is also a wise precaution to reinforce the enterovesical anastomosis with omentum in cases where the bladder pathology is diffuse interstitial cystitis.

When the colon is being sectioned an intravenous injection of either 160 mg gentamicin or 1 g cephradine is given. Afterwards the same drug is continued for the first 5 to 7 post-operative days. Cephradine has lately been preferred as it can be given by mouth as soon as the patient has commenced oral feeding, whereas gentamicin can be given only by the parenteral route. Urethral flow rates should be assessed in all patients prior to surgery. A reduced flow rate in the female is treated by bladder neck dilatation. In the male, either bladder neck resection or bladder neck incision at the 3 and 6 o'clock positions is always required. It is now our practice to resect or incise the bladder neck 2 to 3 weeks before the enterocystoplasty and remove as much prostatic tissue as possible by endoscopic resection in all patients over the age of 45. The post-operative complications experienced following colocaecocystoplasty are shown in Table 2.

Table 2 Post-operative Complications

	Caecocystoplasty	*Colocystoplasty*
External urinary fistula	6	2
Wound disruption	2	–
Incisional hernia	4	–
Intestinal obstruction from adhesions	1	–
Bladder outflow obstruction	5	–
Contraction of cystoplasty anastomosis	1	–
Enuresis	11	–

Results

A result was considered excellent when the patient experienced no dysuria, a diurnal frequency of 3 h or more and nocturia once or very occasionally twice; 78% of patients achieved this criterion. Ten patients in this series died (Table 3). Results for interstitial cystitis are shown in Table 4 and for tuberculosis in Table 5. The improvement in bladder capacity in all of those patients for whom it was available is shown in Table 6. The 6 patients

Table 3 Analysis of Mortality

Patients	*Age*	*Cause of death*	*Time of death after cystoplasty*
W.G.	20	Paralytic ileus	3 days
E.G.	58	Faecal fistula	4 weeks
L.O.	64	Ruptured aortic aneurysm	6 weeks
A.G.	57	Renal failure	15 months
E.N.	66	Myocardial infarction	2 years
K.E.	48	Carcinomatosis	5 years
J.C.	48	Renal failure	5 years
A.T.	64	Intestinal perforation	11 years
			Time of death after colocystoplasty
B.S.	39	Portal cirrhosis	5 months
J.P.	35	Coronary thrombosis	6th post-operative day

Table 4 Details of Clinical Data Before and After Treatment of Interstitial Cystitis

		Caecocystoplasty—7 cases	
		Before surgery	*After surgery*
Frequency	day	7	2
	night	7	2
Dysuria		7	4
Haematuria		3	1
Small bladder capacity		4	–
Urinary infection		1	–
Renal insufficiency		–	–
Previous surgery	kidney	–	–
	bladder	4	–
Mucus in urine 1 year after surgery		–	6

with a bladder capacity of 150 to 250 ml were all suffering from interstitial cystitis.

The complications were less in the colocystoplasty group; there was no obvious reason for this, although there were far fewer patients treated by this method. Urinary fistula was the most disturbing complication but this has not occurred since a 2-layer closure was adopted and the anastomosis covered with omentum. Enuresis has also been a problem; of the 11 cases in the caecocystoplasty group, 5 recovered spontaneously; of the remaining 6, enuresis was present in 3 before surgery but in 3 it was a permanent complication of the surgical procedure. Intensive urodynamic studies (Abel and Gow, 1978) failed to reveal any local neurological disturbance. This suggested that patients with a history of enuresis should be approached with caution.

Ten patients have died and all have been suffering from tuberculosis. Three (W.G., E.G. and J.P.) were classified as post-operative deaths and the first 2 were due to technical errors. Of the other deaths only 2 (A.G. and J.C.) were attributed to tuberculosis, which had caused severe renal damage before surgery was undertaken.

All of the patients with interstitial cystitis did well, with marked symptomatic improvement. Especially noticeable was the reduction in the severe pain and frequency following surgery, although 4 continued to complain of some discomfort. Up to the time of follow-up there has been no recurrence, although most of the patients complain about mucus in the urine. It is important to differentiate between the 2 types of interstitial cystitis as the treatment is different. In the local type of lesion, the typical stellate Hunner's ulcer on the fundus, an excision of the ulcer with 2.5 cm of healthy bladder gives satisfactory results and normally leaves no more than a third of healthy functioning bladder tissue. If the lesion is a diffuse interstitial cystitis, then as much as possible of the bladder should be removed, leaving only a small area surrounding the trigone. It may be necessary in these cases to reimplant the ureters into the ileum.

All of the patients with tuberculosis were satisfied with the results because of the distressing symptoms prior to surgery and there is little appreciable difference between the 2 techniques. A considerable improvement in frequency and bladder capacity was achieved in nearly all patients. Urinary infection was worrying in the early cases, but as time went on it was found that although the infection persisted it did not spread

Table 5 Details of Clinical Data Before and After Treatment

		Tuberculous cases			
		Colocystoplasty (16)		*Caecocystoplasty (34)*	
		Before surgery	*After surgery*	*Before surgery*	*After surgery*
Frequency	day	16	2	34	3
	night	16	3	34	2
Dysuria		13	1	30	4
Haematuria		7	–	12	–
Small capacity bladder		16	1	34	2
Urinary infection		2	2	12	12
Renal insufficiency		8	7	21	15
Previous surgery	kidney	7	–	21	–
	bladder	4	–	–	–
Mucus in urine 1 year after surgery		–	12	–	26
Enuresis		–	–	3	11

Table 6 Pre-operative and Post-operative Bladder Capacity

	Pre-operative	*Post-operative*
30-50 ml	10	0
50-100 ml	16	0
100-150 ml	13	1
150-250 ml	6	2
250-500 ml	0	35
500-1000 ml	0	7

to the upper urinary tract. In the caecocystoplasty cases 50% were symptomless and these were not treated since both the human body and the organism appeared to achieve an affinity which allowed them to exist together without developing an inflammatory reaction. All of the patients with infection were closely watched and, if symptoms developed, prolonged courses of the appropriate antibiotics were begun. Renal insufficiency is no contraindication to this procedure. Our experience agrees with that of Küss *et al.* (1970) and contradicts that of Smith *et al.* (1977) and it is suggested that patients with a creatinine clearance of more than 10 ml/min can be accepted for enterocystoplasty. It should be noted that in the present series the renal function of 6 patients improved after caecocystoplasty; no electrolyte disturbance was found in any patient after either colocystoplasty or caecocystoplasty. Enuresis has remained the biggest problem. Three patients who complained of enuresis before surgery showed no improvement and a further 3 developed the symptoms afterwards. None of these 6 patients responded to any treatment and it is suggested that enuresis is a contraindication to bladder augmentation, especially if there is a history of previous psychiatric disturbance.

Discussion

The difference between bladder augmentation and bladder replacement must be emphasised, as bladder replacement should be used only in cases of carcinoma, in such rare conditions as diffuse interstitial cystitis, or where there has been total chemical or physical destruction of the bladder. All of the patients in this study have treated by augmentation. Ileocystoplasty rformed in only one, a man of 59 in 1969. till alive with some degree of renal failure totally incontinent of urine. However, by wearing a urinal he manages light work and his renal failure is progressing extremely slowly. One case of carcinoma of the fundus of the bladder was treated by caecocystoplasty as the patient refused any conduit. The tumour was an adenocarcinoma of the fundus and the resection was extensive, removing the whole of the bladder down to the trigone but leaving the ureters. He was reviewed for 3 years, when he was fit and well with no secondaries, but he has since been lost to follow-up.

Smith *et al.* (1977) stated that cystoplasty has no place in the treatment of patients with bladder cancer. However, it is believed that this comment is worthy of reappraisal. Table 7 shows some of the published series for bladder replacement by the colon after total cystectomy for bladder tumours. Gil-Vernet and Gosalbez (1957) were among the first to report a total cystoprostatovesiculectomy with colonic replacement for bladder cancer. The patient was voiding with a good stream and no recurrence. Four years later Gil-Vernet *et al.* (1962) reported the results in 41 patients, 15 due to diffuse papillomatosis, 21 infiltrating tumours stages B and C and 5 infiltrating tumours stage D. After 3½ years all of the patients with papillomatosis were alive, but 9 of those with infiltrating carcinoma were dead. Charghi *et al.* (1967) discussed the results in 11 patients; 3 died of recurrent bladder tumours within 2 years of surgery, at the site of the anastomosis; one of the 8 surviving patients developed a recurrence at the site of the anastomosis, 5 years after the colocystoplasty. Bruce (1974) reported 10 cases of carcinoma of the bladder treated by total cystectomy and caecocystoplasty, 8 of which were still alive after 5 years, and Ong (1970) discussed the results in 28 patients treated by total cystectomy and colocystoplasty. Thirteen died within 3½ years but the remaining 12 are alive and are followed up regularly. These results suggest that there may be a place for either colocystoplasty or caecocystoplasty in the treatment

Table 7 Results of Radical Cystectomy Combined with Colocystoplasty for Bladder Cancer

Authors	*No. of cases*	*3½ + survival*
Gil-Vernet *et al.* (1962)	41*	15
Charghi *et al.* (1967)	11	5
Camey (1970)	24	19
Ong (1970)	28	12
Bruce (1974)	10	8

* 15 papillomatosis, 26 infiltrating.

of carcinoma of the bladder and that the procedure may well have been neglected in the surgical approach to this problem. Clearly the cases will have to be carefully selected and a cautious policy adopted; otherwise the failures will be many and a technique that could be valuable will rapidly fall into disrepute, but it would seem to be a reasonable alternative for those cases of recurrent diffuse papillomatosis with limited penetration of the bladder wall.

Recently Leong (1978) has suggested using the stomach for bladder augmentation or replacement, pointing out that the pyloric antrum functions well in the urinary tract, has a good blood supply, good contractibility and acidification properties. He treated 6 patients with long-standing tuberculous cystitis by bladder augmentation; all are alive and well. Following cystectomy for well differentiated transitional cell carcinoma 9 patients were treated by bladder replacement and 4 are still alive after periods ranging from 18 months to 6 years. In this same article a warning was issued that the part of the stomach used should be restricted to the pyloric antrum because of the disastrous consequences when the body of the stomach is employed. Whether or not this technique will replace the existing tried methods of colocystoplasty or caecocystoplasty only further experience can decide, but it is a technique worthy of consideration, especially in patients with intractable fibrophosphatic cystitis who have a persistently alkaline urine.

It is concluded that colocystoplasty and caecocystoplasty are satisfactory methods of bladder augmentation or replacement. The caecum is preferred when the ureters have to be anastomosed as the ileum produces a better conduit; otherwise there is little to choose between the 2 techniques. In cases of bladder carcinoma, enterocystoplasty is worthy of consideration in carefully selected cases. Gastrocystoplasty is a new technique which requires further evaluation before it can be considered as an alternative to the present proven existing methods.

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"Undiversion" with Colocystoplasty for Neurogenic Bladder. A Report of 2 Cases

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Summary—The encouraging success of partial replacement of the bladder for interstitial cystitis and for contracted bladder due to tuberculosis, and the relative success of total bladder replacement for carcinoma, prompted an attempt to reconstruct a bladder in 2 patients with neuropathic bladders, who had problems with their ileal conduit and, thus, "undivert" them. Bladder reconstruction in these patients was performed using a modified technique of colocystoplasty. One of the patients has had 2 normal pregnancies since colocystoplasty.

Attempts to reconstruct a functional bladder for patients with hypotonic neuropathic bladders, due to lower motor neurone lesions, have been described before. Recently they have been attended by varying degrees of success, although earlier investigators believe that such operations have only limited applications (Goodwin and Winter, 1959; Gregoir, 1961; Cibert and Cibert, 1962; Hradec, 1964; Bitker, 1966; Grasset, 1967; Turner-Warwick and Ashken, 1967; Küss *et al.*, 1970).

The previously described operations have involved replacement of the bladder with ileum, caecum or colon—used as tails, horns, patches, etc.—but our technique was first described by Ong (1970) and, with modifications, outlined in a previous article (Bruce, 1973).

Colocystoplasty, originally described by Rubin (1948), is an operation most often performed for contracted bladder due to tuberculosis, interstitial cystitis, and after total cystectomy for carcinoma: it probably represents the most physiological form of bladder replacement to date.

Since 1968, colocystoplasty has been used by one of the authors (P.T.B.) in a total of 33 cases —20 for bladder cancer (Bruce, 1973), 11 for interstitial cystitis (Bruce *et al.*, 1977) and the following 2 cases.

Case Reports

Case 1. A 36-year-old, single Mauritian male presented to this hospital for help with management of his ileal conduit. He had been involved in a motor vehicle accident 13 years previously and sustained a fracture of the lumbar spine which required open reduction. Several years later he developed difficulty with micturition and recurring urinary tract infection; he was found to have a hypotonic neuropathic bladder due to a partial cauda equina lesion and he had a transurethral bladder neck resection. However, because of uraemia, persisting infection, gross bilateral upper tract dilatation and incontinence, he subsequently required an ileal conduit diversion which he had had for 4 years. He did not tolerate this well. Recurring infection, bleeding from the stoma and occasional abdominal cramps required continual and frequent medical attention. His libido was normal and he was still capable of achieving erections but he found his ileal stoma and collecting appliance intolerable. He became extremely depressed and, finally, suicidal.

Neurologic examination disclosed no weakness or sensory loss in the legs but there was decreased sensation to touch and pinprick in the perianal skin (S.5), the anal sphincter was lax and there was no definite voluntary contraction of the perineal floor. "Undiversion" and colocystoplasty were decided upon in October 1975. Initial investigations showed that he had a chronic urinary tract infection despite continuous antibiotic therapy, but his biochemical profiles had returned to normal values (serum creatinine 110 mmol/l, serum urea 6.4 mmol/l, serum potassium 3.8 mmol/l).

Intravenous urography (Fig. 1) showed fairly good function in both kidneys but moderate hydronephrosis of the left and chronic pyelonephritis in the right. A cystogram (Fig. 2) demonstrated the typical "Christmas-tree" pattern of a neuropathic bladder which failed to empty despite repeated attempts at voiding (Fig. 3).

After preliminary endoscopic assessment, operation was undertaken. This involved the removal of 90% of the bladder with preservation of the trigone and the

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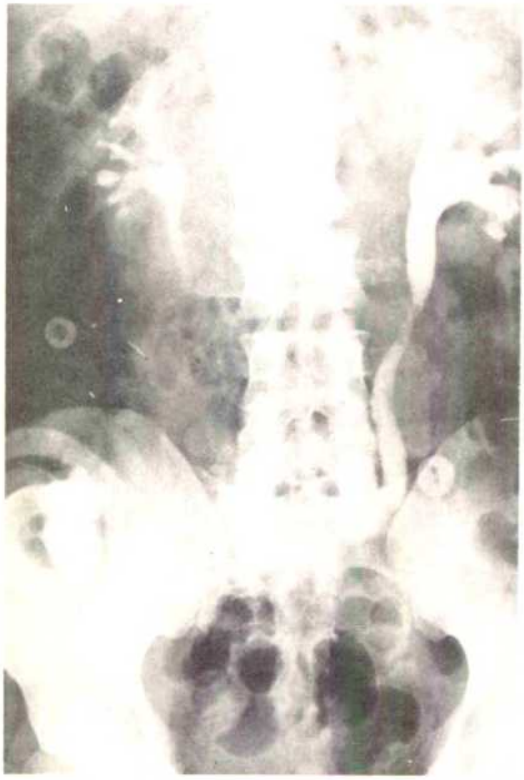

Fig. 1 Case 1. Intravenous urogram shows good function but early hydronephrosis of the left kidney and evidence of chronic pyelonephrosis in the right kidney—one year prior to colocystoplasty and 2 years after ileal diversion.

prostate in an attempt to conserve what continence he had, and potency. The sigmoid colon was isolated on its mesentery and then opened and refashioned into a bladder, using the previously described technique (Ong, 1970; Bruce, 1973). The neck of the new "bladder" was sutured to the remaining trigone and the ileal conduit was taken down and discarded. The ureters were reanastomosed to the fundus of the new bladder, using the Leadbetter antireflux technique.

The patient's post-operative recovery was rapid and uncomplicated and he was discharged on the eighteenth day.

For 18 months after the operation he was able to void with a normal pattern and with only a small amount of residual urine. Post-operative intravenous urography (Fig. 4) at 6 months shows some deterioration of the function of the right kidney, with the condition of the left kidney remaining stable. The micturating cystogram (Fig. 5) demonstrates absence of ureteric reflux, even with severe straining. The post-micturition film was taken after voiding in a sitting position and shows little residual urine (Fig. 6). He was continent during the day but was incontinent at night and had to wear a penile clamp.

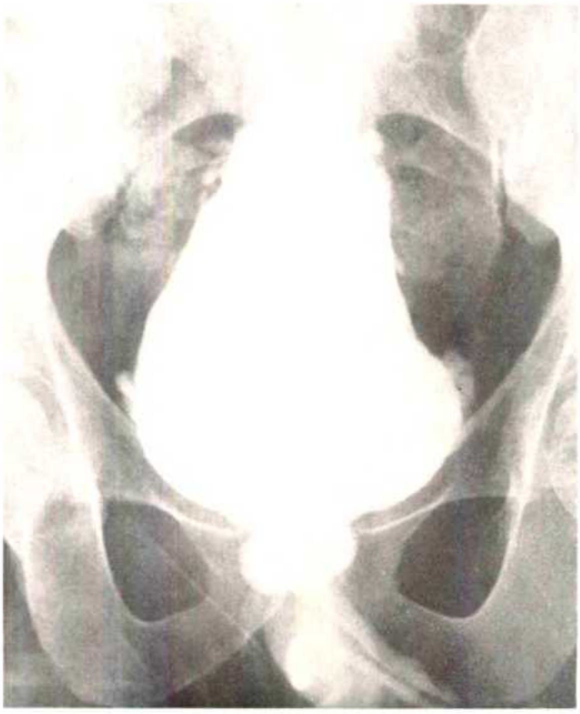

Fig. 2 Case 1. Pre-operative cystogram showing the "Christmas-tree" pattern of the hypotonic neurogenic bladder.

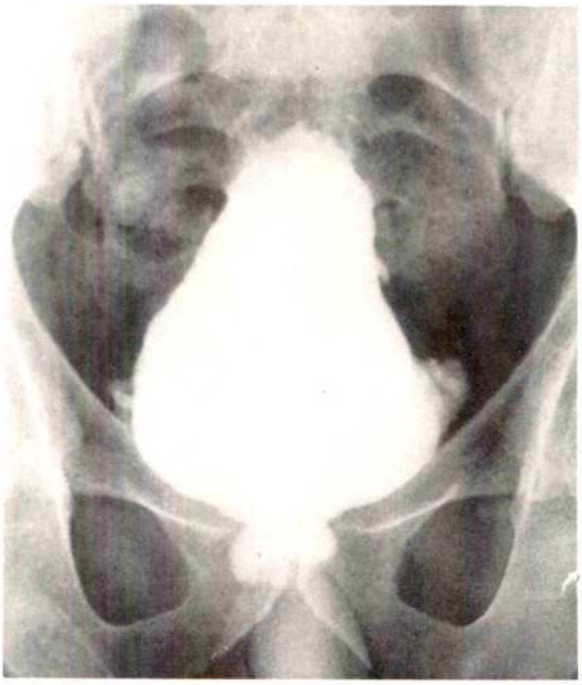

Fig. 3 Case 1. Pre-operative cystogram of this paralysed bladder shows failure to empty despite frequent attempts at micturition.

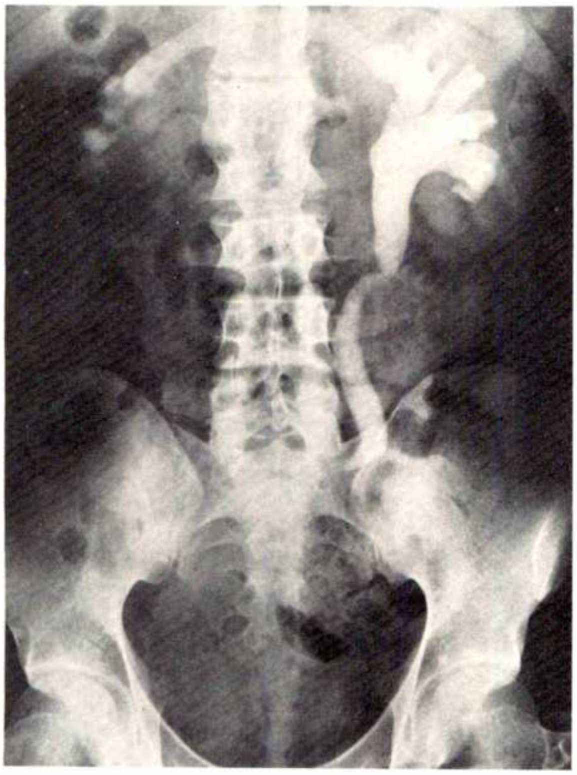

Fig. 4 Case 1. Intravenous urogram 18 months after colocystoplasty shows some deterioration of function of the right kidney while the left kidney shows no changes.

Urine cultures have remained sterile in the 3½ years since the operation without the need for antibiotics, and his biochemical profiles have remained normal.

However, after 18 months his residual urine increased in amount and has remained unacceptably high in spite of a further transurethral bladder neck resection. This increase was accompanied by worsening of the nocturnal incontinence and development of stress incontinence during the day when the bladder is full. He was therefore instructed in self-catheterisation and with twice daily catheterisation he is completely continent, day and night.

The psychological improvement was the most striking and, to us, the most pleasing feature in this case. Even with intermittent self-catheterisation this patient now leads a much happier life and has normal sex.

A cystometrogram shows spontaneous waves of contraction in the colonic bladder commencing at a volume of 400 ml, giving rise to bladder pressure of 50 cm H_2O. These waves are accompanied by a sensation of bladder fullness. Voiding at a peak flow rate of 12 ml/s was achieved by assuming a sitting position, waiting for a wave of contraction and raising the intra-abdominal pressure by straining. A urethral pressure profile shows a low maximum urethral closure pressure of 28 cm H_2O and a profile length of 3.5 cm. The urethral pressure

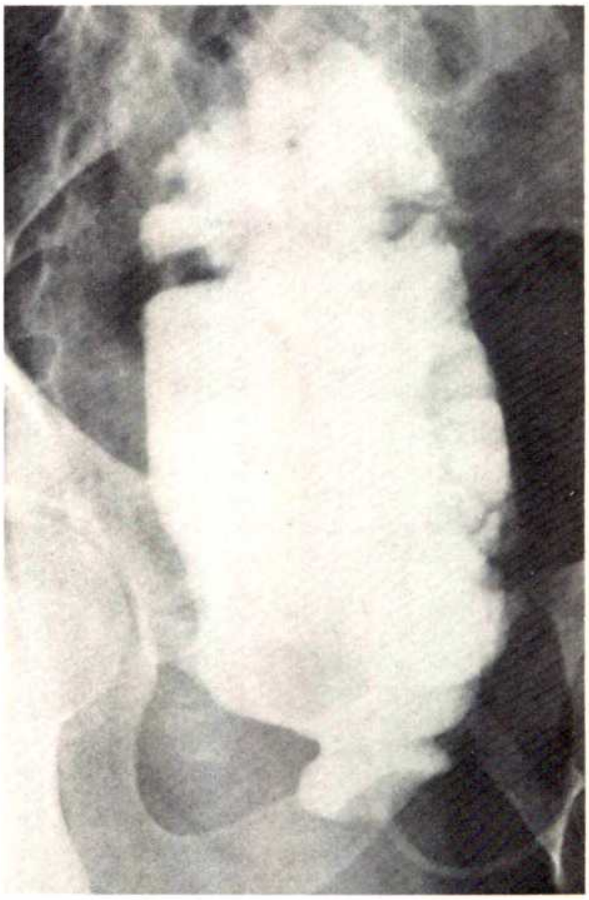

Fig. 5 Case 1. Post-operative micturating cystogram shows haustral pattern of the colocystoplasty.

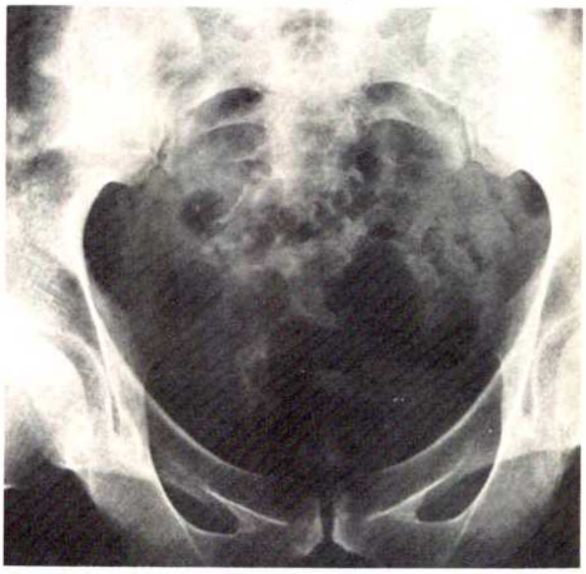

Fig. 6 Case 1. The post-micturition film shows the absence of reflux and good emptying.

is similar in magnitude to the pressure increases which occur in his bladder with coughing and straining and persuaded us not to attempt to lower his post-voiding residual urine by further sphincter surgery because of the risk of total incontinence.

Case 2. A.C., a 24-year-old female, presented 3½ years ago with recurrent urinary tract infection and an ulcerated ileal conduit stoma. She was born with a spina bifida and meningocele which was repaired at the Royal Children's Hospital, Melbourne, when she was 7 months old. Every time she cried there was faecal soiling but the lower limbs were not severely affected and she had only minor deformities of the feet which did not prevent her walking normally. At the age of 6 years an ileal conduit urinary diversion was performed for a neurogenic bladder and total incontinence at the same hospital. One year prior to presentation the ileal conduit stoma required refashioning owing to its regression and stenosis. Over the past few years the patient had experienced recurring loin pain on both sides due to proven urinary tract infections which were managed with a variety of long-term appropriate but ineffective antibiotics.

Neurological examination showed diminished sensation to touch and absent sensation to pinprick in the perineal skin but normal muscle power in the lower limbs. The anal sphincter was lax but some voluntary contraction was present. There was no recent history of faecal soiling even with episodes of diarrhoea.

Endoscopy of the ileal conduit showed that stenosis at skin level was considerable, requiring repeated dilatation, and the conduit itself was somewhat redundant and dilated. An X-ray of the ileal conduit after introduction of radio-opaque dye confirmed dilatation of it as well as both ureters which refluxed freely but also drained freely. An intravenous urogram (Fig. 7) in July 1975 showed that the left kidney was slightly smaller than the right but that there had not been any marked changes since intravenous urography one year previously. There was, however, dilatation of the upper urinary tract with dye persisting in each collecting system at 3½ h. The biochemical profiles were within normal limits with serum urea 3.5 mmol/l and creatinine of 100 mmol/l.

The patient had been managing with a collecting appliance of various designs for the previous 16 years, had been married 1 year and had led a relatively normal sex life. She had never been pregnant.

In view of the apparently previous successful case of conversion from an ileal conduit to a colonic bladder, the possibility of this operation was put to the patient and her husband as an alternative to a life of urinary diversion (with its problems becoming more troublesome). It was made clear to the patient that the colonic bladder may have to be reconverted to an external drainage system should there be evidence of renal deterioration, or should her new bladder be incontinent.

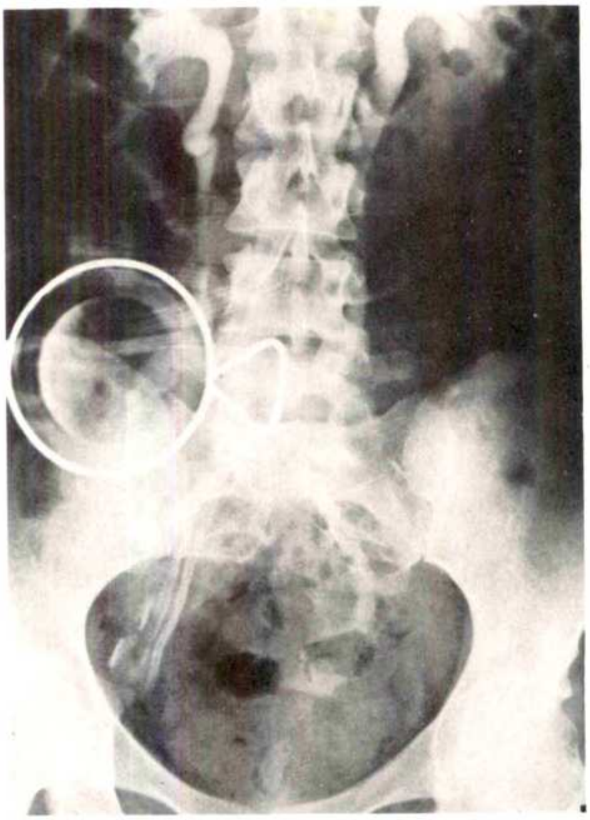

Fig. 7 Case 2. Intravenous urogram—pre-operative.

With this in view, the bladder, which had not been removed at the time of the urinary diversion, was filled with contrast and a cystogram performed. A characteristic "Christmas-tree" contracted bladder was seen (Fig. 8) and after filling the bladder with saline to 100 ml, when suprapubic discomfort was felt, the patient was asked to walk about and was able to retain this volume for 1 h. She was continent but could not void.

This clinical assessment, supported by cystometrogram findings, suggested that normal detrusor function was lost and that the bladder had contracted considerably, but the possibility of continence remained.

After a period of 9 months, during which time the patient was constantly reviewed, she decided to undergo colocystoplasty. In November 1976 the majority of the bladder was removed and the colonic bladder fashioned and anastomosed to the trigone as in Case 1. The ureters were reimplanted into the new bladder using a similar antireflux technique and the ileal loop discarded. The post-operative period was uneventful and after 14 days in hospital the patient was discharged. She was totally continent by day and night and enjoyed the new experience of voiding *per urethram*.

The patient became pregnant and at 8 weeks her control began to deteriorate until eventually she had to

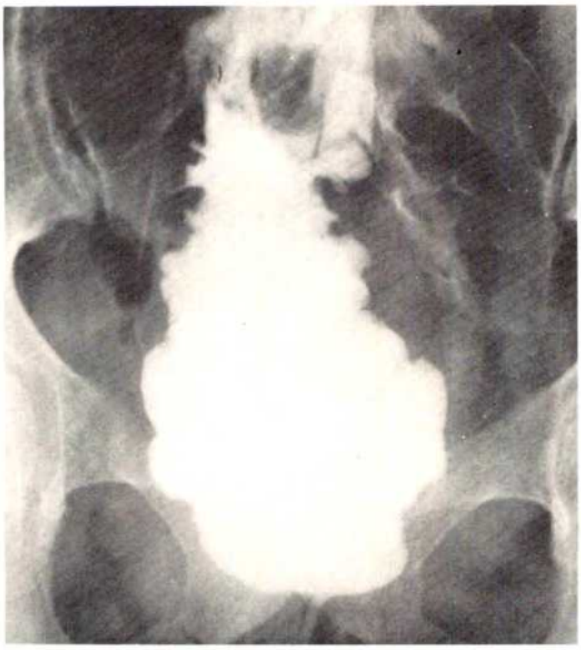

Fig. 8 Case 2. Cystogram of original "Christmas-tree" bladder.

be managed with an indwelling catheter due to incontinence. A catheter specimen of urine was sterile but she was given antibiotic cover during the remainder of her pregnancy while on continuous drainage. At 9 months she delivered a healthy child vaginally, at the same time expressing her Foley catheter. From this moment, and for the next 8 months, she was totally continent once more. Occasionally she experienced stress incontinence on excessive straining, but otherwise was dry. An intravenous urogram during this period (Fig. 9) showed, if anything, a slight diminution of ureteric dilatation compared with the pre-operative X-ray. Again she became pregnant and at 12 weeks lost her control.

Catheterisation confirmed an empty bladder, there being no question of retention with overflow (the enlarged uterus occupying the pelvis presumably did not allow the colonic bladder to fill). She was managed through her second pregnancy in the same way as the first and at term delivered vaginally of a healthy baby.

It is now 2½ years since colocystoplasty and she regards herself as fully continent. She voids every 1½ to 2 h and has occasional stress and urge incontinence. She is free of infection and voids with 100 to 200 ml residual urine. A filling cystometrogram shows no evidence of spontaneous contraction in the colonic bladder, but she has a vague sense of filling in the new bladder. Capacity is approximately 600 ml. Increases in intra-abdominal pressure are not fully reflected in pressure rises in the bladder. A voiding pressure study (Fig. 10) shows that micturition is accomplished entirely by raising the intra-abdominal pressure. The urethral pressure profile shows a very low maximal urethral closure pressure of 10 cm H_2O.

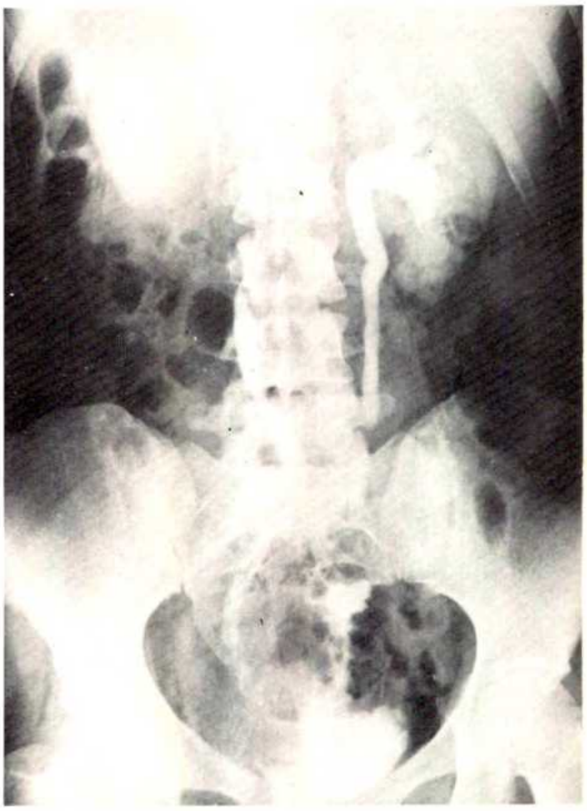

Fig. 9 Case 2. Intravenous urogram 15 months after colocystoplasty and 4 months after delivery of first child.

Discussion

The principal reason for performing this operation on these 2 patients was an unsatisfactory result from urinary diversion. The first patient had

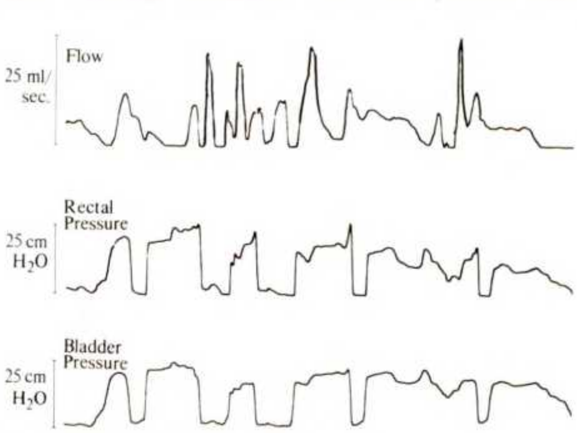

Fig. 10 Case 2. Voiding pressure study.

severe psychological disturbances and wished to be rid of his external drainage appliance. The second had problems with her conduit which were severe enough to seek an alternative. The decision to "undivert" to a colocystoplasty was prompted by the finding of minimal neurological lesions at cauda equina level, which suggested the possibility of continence, as did the preservation of some sensation in the bladder base. On the other hand, a low bladder outflow resistance is necessary to allow emptying of a colonic bladder, mainly produced by increased intra-abdominal pressure. The spontaneous waves of pressure produced by peristalsis in response to distension in the colonic bladder are not sustained at lower bladder volumes before or during emptying.

Further experience is necessary to see if urethral pressure studies can select patients who would be continent following bladder reconstruction in this way. It is surprising that Case 2 is so continent.

The deterioration in function of the right kidney in Case 1 may be iatrogenic in origin, but since he has been free of loin pain and had considerable scarring of the right kidney initially, we believe that this is more likely to be due to progressive intrinsic renal disease. Reasons for previously reported failures with cystoplasty for neurogenic bladder have included defective emptying due to a spastic external sphincter and, we believe, the use of ileum instead of colon. This feeling is shared by other authors (Küss *et al.*, 1970).

It was made perfectly clear to the patients that they may require further surgery should renal function deteriorate in the future and that reversal to external drainage would be a straightforward procedure, using the fashioned colon as a conduit. No such deterioration, however, has occurred up to 3½ years post-operatively in the first case and 2½ years in the second.

Acknowledgements

We wish to thank Mr A. B. G. Carden for his part in the isolation of the sigmoid colon on its mesentery and the reconstitution of the large bowel by colorectal anastomosis in these 2 cases.

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Transection of the Bladder as a Method of Treatment in Adult Enuresis Nocturna

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Summary—Ten adults with enuresis were treated by bladder transection. Urodynamic assessment was carried out before and after the operation. No significant urodynamic changes were recorded following transection. However, good results were obtained in 5 cases and improvement in 2.

Frequency of micturition during the day, nocturia and nocturnal incontinence or enuresis may be caused by overactivity of the parasympathetic nervous system. Selective denervation of the detrusor for severe, persistent urgency was attempted by supratrigonal transection of the bladder by Turner-Warwick and Ashken (1967). In 1970 Yeates introduced the procedure for severe enuresis persisting into adult life. Turner-Warwick and Ashken (1967) divided the inferior vesical arteries, whereas Yeates transected only the detrusor. Further results were reported recently by Hindmarsh *et al.* (1977) and Parsons *et al.* (1977). Both groups described good results in over 50% of their cases. In many instances the history and physical examination provided sufficient information for the diagnosis to be made, but some patients required further urodynamic assessment to differentiate between those without evidence of bladder dysfunction and those with overactivity of the detrusor, which may be the primary cause of their enuresis. We report the urodynamic findings and clinical effects of bladder transection in 10 cases of adult enuresis.

Patients and Methods

Ten adults with longstanding enuresis were investigated urodynamically before and after bladder transection. There were 5 females and 5 males aged between 19 and 31 years. The technique of transection described by Essenhigh and Yeates (1973) was adhered to in all cases. All patients were discharged from hospital within 14 days of operation. No complications were encountered with infection or bladder emptying.

Case Reports

Case 1. M.B.: 31-year-old male. Primary nocturnal enuresis with daytime frequency. Transurethral resection bladder neck aged 17; no effect. Temporary improvement with Orphenadrine and alarm buzzer. Capacity 400 ml. Uninhibited contractions on cystometry. Bladder transection May 1974 effective for 6 months, then enuresis recurred on alternate nights. Daytime frequency persisted. Cystometry 6 months after operation was unchanged.

Case 2. A. de V.: 24-year-old female. Primary enuretic with no diurnal symptoms. Many forms of therapy resulted in only temporary relief. Psychiatric treatment aged 20 to 22 years. Pre-operative capacity 400 ml. Cystometrically stable. Transection May 1975. Dry for 3 months then relapsed. No improvement.

Case 3. H.S.: 20-year-old male. Nocturnal enuresis with no diurnal symptoms; wet every night except when

Table

Clinical type	*Pat. No.*	*Urodynamic abnormality*	*Results*
Enuresis nocturna			
	2	–	no change
	3		improvement
	5	–	good
	7	+	good
	8	–	good
	9	–	good
Enuretic syndrome			
	1	+	some improvement
	4	–	good
	6	+	no change
	10	+	no change

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away from home. Medical treatment unsuccessful. Patient refused urodynamic assessment. Transection January 1975. Dry for one month followed by partial relapse. Slight improvement.

Case 4. G.S.: 20-year-old female. Nocturnal enuresis with diurnal frequency. Capacity 650 ml; cystometrically stable. Transection November 1974. No further enuresis or diurnal symptoms. Assessment 6 months post-operatively: capacity 700 ml; stable.

Case 5. H. van. U.: 22-year-old female. Primary nocturnal enuresis. Medical treatment ineffective. Capacity 500 ml; cystometrically normal. Transection October 1974. No further nocturnal enuresis. Post-operative assessment: capacity 550 ml; stable.

Case 6. M.K.: 31-year-old male. Bedwetting twice weekly. Nocturia and frequency. Treatment unsuccessful. Urodynamic assessment: capacity 500 ml; uninhibited contractions present. Transection March 1976. Three months after operation nocturnal incontinence occurred only after taking alcohol, after which bedwetting returned to previous rate. Post-operative urodynamic assessment: no change. Daytime symptoms reduced.

Case 7. M. van W.-C.: 20-year-old female. Nocturnal incontinence most nights, persisting after marriage. No diurnal symptoms. Temporary success with buzzer alarm. Capacity 450 ml with uninhibited contractions. Transection May 1975. Initially incontinent at night for one month followed by progressive improvement.

Case 8. A. v/d H.-vanR.: 24-year-old female. Incontinent every night except during pregnancy. Urodynamic assessment 1973; capacity 240 ml; stable. Dry during 1974 but intermittent periods of incontinence during 1975. Urodynamic assessment 1975: capacity 400 ml; uninhibited contractions. Transected May 1975; dry afterwards. Post-operative urodynamic assessment: capacity 450 ml; stable.

Case 9. J.D.: 20-year-old male. Primary nocturnal enuresis. Temporary relief with imipramine. Capacity 770 ml; hypertonic on cystometry. Transection October 1975. No further enuresis. Post-operative urodynamic assessment unchanged.

Case 10. E. van H.: 19-year-old male. Primary nocturnal enuresis. Wet every night. Medical treatment failed. Cystometry aged 8; capacity 175 ml; hypertonic pressures. Urodynamic assessment 1974: capacity 460 ml; uninhibited contractions. Bladder transection February 1975. April 1975: incontinent every night except when away from home. Urodynamic assessment 1976: capacity 500 ml; uninhibited contractions as pre-operatively. Operation unsuccessful; daytime frequency as pre-operatively.

Results

The patients were divided into 2 groups:

1. Four patients with the enuretic syndrome of nocturnal enuresis and daytime frequency and urgency.
2. Six patients with nocturnal enuresis alone.

Enuretic Syndrome

One patient had complete remission of nocturnal and diurnal symptoms. Another showed improvement and the remaining 2 patients remained unchanged.

Nocturnal Enuresis

Good results were obtained in 4 patients, one showed improvement and one remained unchanged. The single female with the poor result was aged 24 and had a psychiatric history. Recurrence of her nocturnal incontinence was related to further psychiatric problems.

Urodynamic Evaluation

Patients exhibiting uninhibited contractions and hypertonic pressures were those with the enuretic syndrome. There was little change between pre-operative and post-operative urodynamic assessments, although in some cases a slightly higher bladder capacity was recorded post-operatively. Gibbon *et al.* (1973) referred to this increase in bladder capacity and delay in the development of higher pressures as a "a shift to the right". Patients with evidence of uninhibited contractions were found after operation to be only slightly improved or to show no improvement at all.

Patients with nocturnal enuresis alone were urodynamically stable both pre-operatively and post-operatively.

Discussion

Spontaneous remission continues after the age of 16 but at a reduced rate from that seen before this age (Miller, 1966; Forsyth and Redmond, 1974). Medical treatment and bladder distension are frequently followed by a symptomatic recurrence (Parsons *et al.*, 1977). In those cases most resistant to therapy it therefore seems justified to transect the bladder. The rationale for this procedure is that the parasympathetic nerves innervate the detrusor and are thus divided by the transection.

Although this study does not show a clear effect on the detrusor after bladder transection, results suggest that some functional alteration does occur. In our series we had 5 complete successes (50%), the patients being dry without diurnal symptoms. It is tempting to suggest that a psychological effect is responsible for this success, but it was evident that patients with psychologically abnormal backgrounds failed to respond to transection. In the psychologically stable group the effect of the operation seemed to suggest some somatic change, although the possibility of a neurotic disturbance cannot be overlooked

Patients with uninhibited detrusor contractions did not appear to be helped by this procedure.

The lack of response in some cases reflects our inability to select accurately those cases which will respond to bladder transection. Until we know more of the patho-physiological processes involved in adult enuresis, and the reason why bladder transection is effective in certain cases, we should limit this procedure to patients with the most intractable form of adult enuresis.

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Subcutaneous *Corynebacterium parvum* in Bladder Cancer

A controlled study of its immunological effects

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Summary—Fourteen out of 26 patients with invasive bladder cancer were randomly assigned to receive weekly subcutaneous injections of *Corynebacterium parvum* (CP) in addition to standard treatment. Peripheral blood T lymphocyte percentage, K cell activity, mitogen responsiveness, and monocyte and polymorph leucotaxis were measured at intervals over a period of 1 to 2 years. The only consistent difference between the CP-treated patients and the controls was a slightly higher level of K cell activity in the former, who, however, fared rather worse than the controls in terms of survival.

Immunostimulatory and macrophage-activating agents like BCG and *Corynebacterium parvum* (CP) are being used in the treatment of human cancer in the hope that they will stimulate any immune response of the patient to his tumour, or will counteract the non-specific immunosuppression and susceptibility to infection associated with cancer or with its treatment by radiotherapy, chemotherapy and surgery (Israël *et al.*, 1975). Little is known of the actual immunological effects of these adjuvants in man. We decided to measure a number of immunological parameters in a small, controlled study of the effect of weekly injections of CP in patients with bladder cancer who were being treated with methotrexate, irradiation and, where possible, cystectomy.

Because the CP was to be given on an outpatient basis we gave it subcutaneously (s.c.) to avoid the very unpleasant systemic reactions produced by intravenous injection (Israël *et al.*, 1975).

As indicators of immune function we measured the chemotactic responsiveness of blood monocytes and polymorphs (since these cells are important defences against infection), the transformation of blood lymphocytes in response to the mitogens PHA and Con A (for thymus-dependent function) and Pokeweed mitogen (for both T (thymus-derived) and B lymphocyte function), the percentage of T lymphocytes in the peripheral blood and blood levels of cytotoxic "K" cells, which kill tumour target cells in the presence of antibody (Cerottini and Brunner, 1974).

Patients and Methods

All patients who presented over a 2-year period at St Mary's Hospital Urology Department with invasive bladder cancer were invited to join the trial. Those who gave informed consent were assigned randomly to the CP-treated or the control group, randomisation being carried out separately for patients considered to have operable tumours, to avoid weighting the groups. The staff performing the assays did not know which patients were receiving the CP.

The first sample of blood was taken before the start of treatment and the second (one week later), after a 48-hour intravenous infusion of 1 g methotrexate followed by Leucovorin rescue. The first injection of CP, 1 mg (supplied as a suspension of killed strain CN 6134 organisms, 7 mg/ml in 0.01% thiomersalate (by Wellcome Research Laboratories)), was then given subcutaneously. The injection was repeated weekly, into different sites, for 2 years for the first patients to enter the trial, or one year for those

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entering in the second year. Further blood samples were taken at 3-monthly intervals for at least one year. All patients received radiotherapy, starting a week after the first injection of CP and given over a 3 to 5-week period. The doses aimed at were 6000 to 6500 rads for patients with inoperable tumours and 3000 to 3500 rads preoperatively for the others. Cystectomy was performed 4 weeks after radiotherapy.

Immunological Procedures

Highly purified lymphocytes were used as a source of K cells, as phagocytes interfere variably with the antibody-dependent cell-mediated reaction.

The ^{51}Cr-release cytotoxic assay was carried out, using rabbit anti-AKR.A antiserum and a 4 to 6-hour incubation, as fully described by Purves and Brown (1978). The results are expressed as the relative cytotoxic capacity (RCC) of the patient's lymphocytes compared with lymphocytes of a healthy laboratory control assayed at the same time, and given an arbitrary value of one. We also calculated the activity per ml of blood (RCC/ml), using the formula:

$$\text{RCC/ml} = \text{RCC/cell} \times \frac{\text{yield of lymphocytes/ml blood of patient}}{\text{yield of lymphocytes/ml blood of control}}$$

Mitogen responsiveness was measured as described by Berenbaum *et al.* (1976), using PHA (Wellcome purified, 6.125 μg/ml final concentration), Con A (Miles Labs, 1 in 860, final concentration) and Pokeweed mitogen (Gibco Co. Ltd, 5 ml per vial, 1 in 20 final dilution) and 72-hour cultures.

Polymorph and monocyte chemotaxis were carried out using the raft method of Addison and Babbage (1976), in which the cells are incubated in normal human serum.

T lymphocytes were measured by the SRBC-rosetting method of Stjernswärd *et al.* (1972). In all of these assays cells from a laboratory control were also included.

Student's t-test was used to compare the mean values of CP-treated and control groups.

Results

The total number of patients entering the trial over the 2 years was 26, 14 in the CP-treated group and 12 in the control group. The CP was

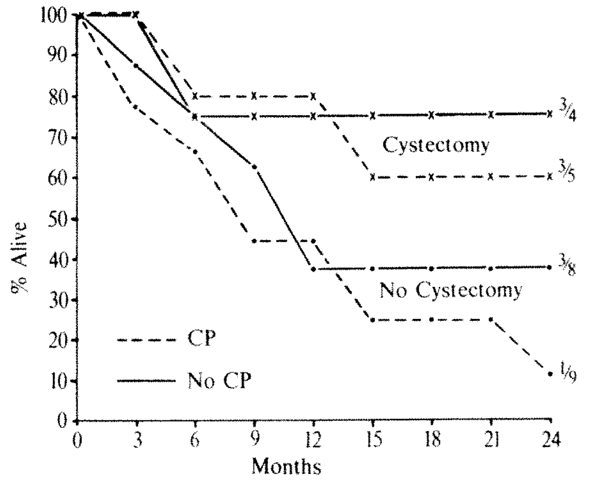

Fig. 1 Percentage survival of CP-treated and of control patients over a 2-year period. Cystectomy patients are shown separately. Numbers given are of 2-year survivors and of total patients in each group.

well tolerated except for the development of painful inflammatory reactions at the site of each injection in one patient, who refused further injections after 6 weeks. Another patient who developed diffuse intravascular coagulation did not improve when the CP was stopped, but did improve following cystectomy.

There were no differences between the 2 groups in terms of age, sex ratio, initial lymphocyte count or tumour staging; 5/14 in the CP-treated and 4/12 out of the control group had a cystectomy.

Figure 1 shows the survival of the patients, followed up for 2 years after entering the trial. The slightly worse survival of the CP-treated group was seen whether patients had operable or inoperable tumours.

The only immunological difference between the CP-treated and control patient groups was the consistently higher mean level of K cell cytotoxic activity per lymphocyte in the CP-treated patient group (Fig. 2). The difference was not, however, statistically significant. The yield of lymphocytes from the blood fell following methotrexate treatment and during radiotherapy (Fig. 2), as expected, but CP treatment had no effect on this. The relative cytotoxic capacity per ml of blood was therefore also higher in the CP-treated group.

Background 3 H-thymidine uptake and mitogen responses are shown in Figure 3. Compared with laboratory controls both groups of patients had

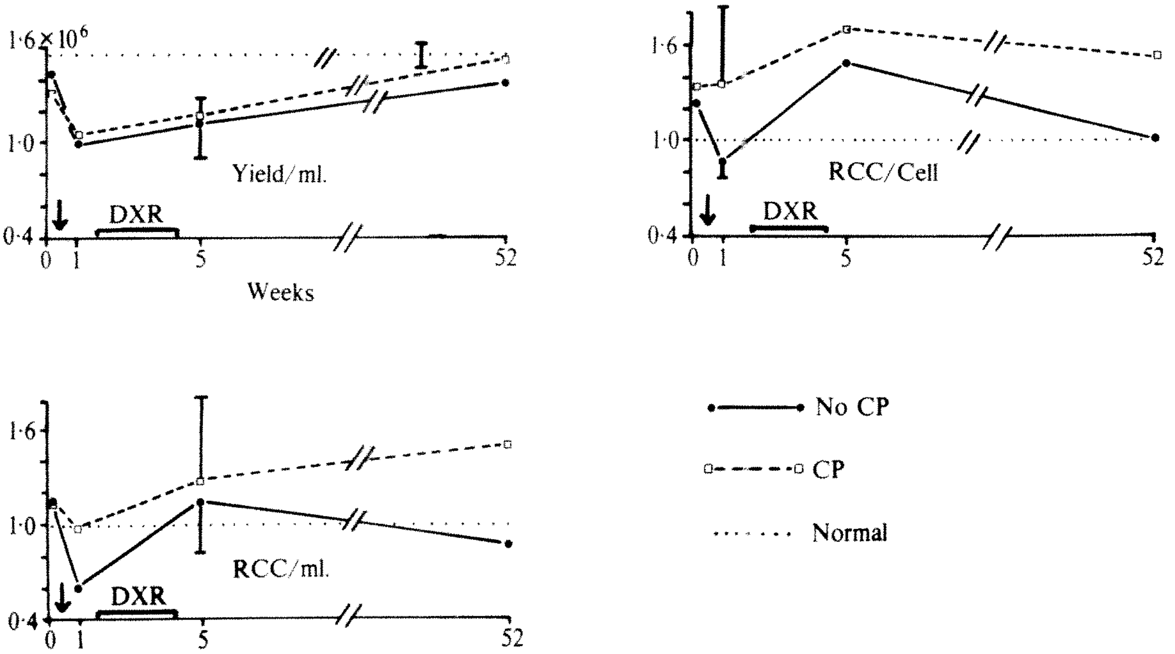

Fig. 2 Time course of the relative K cell activity per cell, the lymphocyte yield per ml of blood, and the relative K cell activity per ml for CP-treated and control patients groups. Activity of normal laboratory controls shown as a horizontal line (=1). Arithmetic means are shown, together with a representative SEM (vertical bars). Arrow indicates methotrexate infusion.

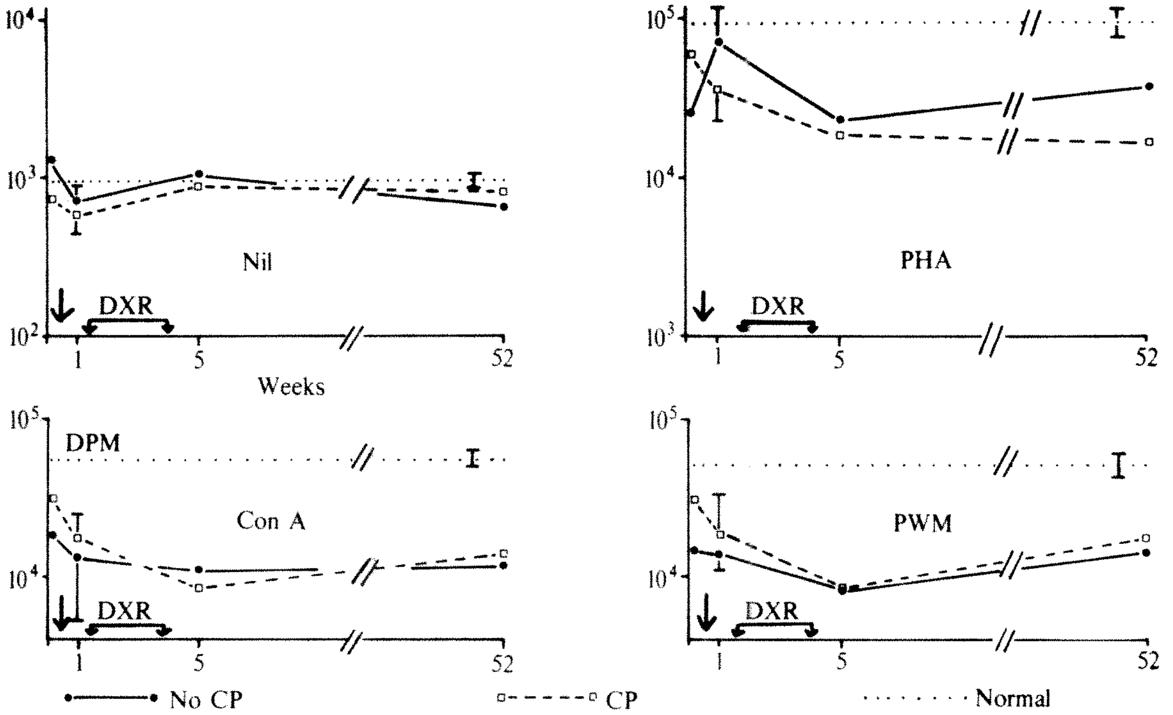

Fig. 3 Time-course of background and mitogen-stimulated ^{3}H-incorporation by peripheral blood cells of CP-treated and control patients. The average ^{3}H-thymidine uptake of laboratory controls is shown as a horizontal line. Geometric means are shown, together with a representative SEM (vertical bars). Arrow indicates methotrexate infusion.

reduced reactivity before treatment, confirming that patients with bladder cancer are immunosuppressed. The further immunosuppression following methotrexate and irradiation can also be seen. There was no indication that the CP-treated group were less immunosuppressed than the control patients.

The chemotaxis of polymorphs or monocytes of patients was no different from that of normal laboratory controls at the beginning of the trial (data not shown). Similarly, the percentage of blood T lymphocytes was the same in normal laboratory controls (mean 68%, standard deviation 15%), CP-treated patients (mean 67% ± 23%) and control patients (mean 70% ± 11%), although one patient receiving CP had a persistently low proportion of T cells (25-40%). Neither chemotherapy, radiation or surgery had any consistent effect on chemotactic responses or T cell percentages.

Discussion

It was not the purpose of this small trial to test the clinical effectiveness of CP, since at least 100 patients would have been needed to demonstrate an increase in survival of as much as 30% (Peto *et al.*, 1976). Nevertheless, our results are discouraging in that there was no suggestion that CP treatment had benefited either the group of patients with the better prognosis (cystectomy group) or that with the poorer, and there was no difference between the 2 groups in the distribution of age, lymphocyte count or tumour spread at the start of the trial which might have obscured a positive effect of CP.

There have been reports of positive clinical effects of CP given intravenously (Israël *et al.*, 1975), as well as negative reports (Gordon, 1978). Our result might show that s.c. CP is less effective than a single intravenous injection (Ghaffar and Cullen, 1977). However, repeated s.c. injections such as we used are perfectly capable of causing macrophage activation in both man and mouse, and result in the appearance of cytotoxic cells in mouse lymphatic organs (Scott and Warner, 1976; Ghaffar and Cullen, 1977; Medenica *et al.*, 1978). The only way to provide conclusive proof of the inferiority of s.c. CP over intravenous CP in man would be a much larger controlled trial comparing the two.

The results of the immunological tests are in accord with those of others in trials of intravenous CP, since most authors find that although mitogen transformation and blood lymphocyte counts fall immediately after CP injection (during the phase of hyperpyrexia and clinical shock), they return rapidly to normal and there is no consistent long-term alteration in these or in the percentage of T lymphocytes in the blood (Minton *et al.*, 1976; Fisher, 1978).

The one interesting finding was the elevated levels of K cells in the CP-treated group. Since we used purified lymphocytes, this was not merely due to increased monocytes in the peripheral blood following CP. Thatcher and Crowther (1978) have described similar K cell increases in man after intravenous CP, and we have also seen it in rats (paper in preparation), so it may be an important consequence of immunotherapy. The exact role of this type of cell-mediated cytotoxicity in tumour defence *in vivo* is not yet clear, but the possession of high levels of these cells did not benefit the CP-treated patients in this trial.

Acknowledgements

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Acute Phase Reactant Proteins in the Clinical Management of Carcinoma of the Bladder

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Summary—The levels of a number of acute phase reactant proteins have been measured in 250 patients with carcinoma of the bladder in all stages. Three of them, acid glycoprotein, antichymotrypsin, and C-reactive protein, frequently gave abnormal results in advanced disease. The levels of these 3 proteins in patients who were clinically tumour-free were not distinguishable from those from an age-matched control group. The levels in patients with T1 and T2 bladder tumours were sometimes elevated. In advanced disease, figures were commonly above the normal range.

The increasing precision and convenience of modern biochemical techniques have led to the identification of several "cancer markers", many of which are proteins. It would clearly be advantageous to the management of bladder cancer to have biochemical measurements of tumour activity to supplement routine methods of assessment which, though precise for local disease in the bladder, are sadly unreliable once the disease has spread.

Various cancers have been shown to produce substances which have clinical values as indicators of tumour progress. These may be oncofetal antigens such as alpha-fetoprotein, which has an established place in the management of hepatoma and of some testicular cancers, and carcinoembryonic antigen (CEA) which has been used to monitor the progress of gastrointestinal cancer; or they may be hormones—the Beta sub-unit of human chorionic gonadotrophin in choriocarcinoma is an obvious example. This subject has been reviewed by Munro Neville and Cooper (1976). On balance the oncofetal antigens have been disappointing as markers in bladder cancer (Nery and Munro Neville, 1976; Turner *et al.*, 1977).

In other cases, information about tumour progress has been obtained by observing the host's response. The acute phase reactant proteins (APRP) are a group of specific proteins, synthesised and degraded in the liver, the levels of which change in response to stimuli from injury, infection or cancer in a way which is poorly understood but whose profile may be specific to the stimulus. They reflect the increasing tumour load in gastrointestinal carcinoma, for example (Mackay *et al.*, 1974; Munro Neville and Cooper, 1976).

The contribution of measurement of APRP levels to the clinical management of patients with carcinoma of the bladder has not been fully assessed, although ratios of the levels of certain serum proteins have been suggested as providing the basis of a "cancer index" (Hollinshead *et al.*, 1977).

Materials and Methods

Measurements of APRPs were made on serum samples drawn from more than 250 patients being investigated and treated for bladder cancer, and from 106 control subjects with a similar age and sex distribution. Of these, 83 were asymptomatic patients seen for review following relief of prostatic obstruction (64 cases) or after treatment of urinary infection (19 cases). Seven were men over 40 years of age attending for vasectomy, and the remaining 16 had miscellaneous, non-acute urological conditions. At the time of sampling the subjects were not infected, did not have urinary retention and had not been recently anaesthetised. The results in the bladder cancer patients were correlated with the clinical state of the

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disease. No retrospective change in the assessment was made, even in cases in which the subsequent course made it clear that it might have been optimistic.

Serum was separated within 4 h and stored at −20°C until analysed.

To select the combination most likely to yield information of clinical value, measurements were initially made of the levels of a number of serum proteins. These included albumin, acid glycoprotein (AGP), alpha-1-antitrypsin (AT), antichymotrypsin (ACT), C-reactive protein (CRP), haptoglobin (HPT), and prealbumin (PAB). Analysis of the preliminary data showed that 3 proteins (AGP, CRP, and ACT) reflected the clinical state of the disease more closely than the others, which had a relatively lower yield of abnormalities even in advanced disease. Further study was therefore concentrated on these 3 proteins.

Biochemical Techniques

The APRPs and serum albumin were measured by single radial immunodiffusion using reagents and standards obtained from Behringwerke, Marburg/Lahn, West Germany. The day-to-day plate variation was tested by repetitive measurements of sera known to be in the high, middle and low range values for each of the 3 proteins. The percentage variation (SD/Mean × 100) was as follows: AGP 7%, ACT 6% (Kelly *et al.*, 1978). In view of these figures and the high correlation coefficient between AGP and ACT measurements, each measurement was done as a single estimate.

Results

Stability and Definition of "Normal" Limits

The levels of ACT, AGP, and CRP were stable in tumour-free patients. Six subjects had serial specimens taken at intervals while in remission. The average variations around the patient's own mean were as follows:

ACT: 0.0467 g/l, ±7.1% (n = 26)
AGP: 0.08 g/l, ±12.9% (n = 26)

The stability of CRP measurements cannot be established by this method as it has a normal mean value of only 2.2 mg/l and it is well established that at levels of less than 5 mg/l the radial immunodiffusion assay becomes inaccurate. None of the CRP values from these 6 patients was greater than 12 mg/l.

The level of each protein was found to rise in advanced carcinoma of the bladder. It is thus necessary to establish "normal" levels for each protein which are unlikely to be exceeded in the absence of active disease. It was not appropriate to do this by calculating the standard deviation of the mean as the distribution of normal values was markedly skewed in the case of CRP, and was significantly different from the Gaussian distribution in ACT and AGP. Accordingly, limits of normality were established arbitrarily by inspection of the data from control groups and from tumour-free patients, selecting a level which was exceeded by approximately 1 in 20 of the "normal" population (Tables 1, 2 and 3).

Control Group and Tumour-free Patients

Two sets of control data were available for comparison with tumour-bearing patients. The first

Table 1 The Frequency of Elevated Serum Acid Glycoprotein (AGP) Levels in Control Subjects and Tumour-free Patients

	Number	*Abnormals ≥ 1.25 g/l*
Controls	106	4 (3.8%)
T1 free*	270	12 (4.4%)
T2 free	48	–
T3 free	83	3 (3.6%)
T4 free	38	1 (2.6%)
Totals	545	20 (3.7%)

Mean = 0.81 g/l.
Median = 0.8 g/l.

* "T1" indicates the state of the disease at diagnosis. "Free" indicates that there was no clinical evidence of persistent disease at examination immediately after the sample had been withdrawn.

Table 2 The Frequency of Elevated ACT Levels in Control Subjects and Tumour-free Patients

	Number	*Abnormals ≥ 0.75 g/l*
Controls	–	–
T1 free	60	1 (1.7%)
T2 free	11	1 (9%)
T3 free	45	–
T4 free	27	–
Totals	143	2 (1.4%)

Mean = 0.497 g/l.
Median = 0.5 g/l.

Table 3 The Frequency of Elevated CRP Levels in Control Subjects and Tumour-free Patients

	Number	*Abnormals* *≥12 mg/l*
Controls	70	2 (2.9%)
T1 free	258	7 (3.7%)
T2 free	43	1 (2.3%)
T3 free	77	8 (11.4%)
T4 free	38	-
Totals	486	18 (3.7%)

Mean = 4.0 mg/l.
Median = 3.0 mg/l.

was from subjects who had never had carcinoma of the bladder, and the second from those who had had the disease but were clinically free of tumour at the time of examination. The data from both groups are presented in Tables 1, 2 and 3, showing the percentage of readings exceeding the arbitrarily defined normal levels (1.25 g/l for AGP; 0.75 g/l for ACT; 12 mg/l for CRP).

The levels from patients who had had bladder cancer but were tumour-free at the time of the examination tended to have a slightly higher mean than those from subjects never having had bladder cancer, but the difference was small and not significant ($P = >0.99$).

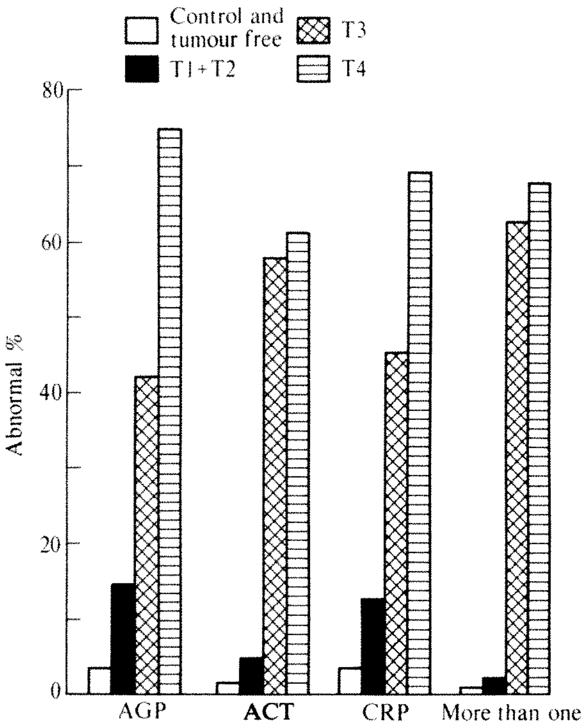

Fig. 1 The percentage of abnormal readings at different T categories (AGP, ACT, CRP, and any combination).

Table 4 The Frequency of Elevated AGP Levels in Patients With Bladder Cancers at Various T categories

	Number	*Abnormals* *≥1.25 g/l*
Controls + T free	545	20 (3.7%)
T1 +ve	170	30 (17.6%)
T2 +ve	82	6 (7.3%)
T1 + T2 +ve	252	36 (14.3%)
T3 +ve	64	27 (42.2%)
T4 +ve	104	78 (75.0%)

Patients with Active Bladder Cancer: T1 and T2 Tumours

Approximately 225 readings were available from patients with low category bladder tumours (T1 and T2). The figures are shown in Figure 1 and in Tables 4, 5 and 6. It can be seen that the incidence of abnormalities was greater in patients with T1 and T2 bladder tumours than in those who were tumour-free (for AGP and CRP $P = <0.001$, ACT not significant).

Patients with Active Bladder Cancer: T3 and T4 Tumours

Approximately 60 readings were available from patients clinically judged to have T3 tumours and approximately 80 from patients with T4 lesions. Figures for these categories are also presented in Tables 4, 5 and 6 and in Figure 1. It is clear that the frequency of abnormality is much greater in patients with T3 tumours than in those with lower category disease ($P = <0.001$ for all 3 proteins). The proportion of abnormalities rises further when the T4 stage is reached. Figures 2, 3 and 4 show the changes in distribution of AGP, ACT and CRP in patients with different category disease.

Table 5 The Frequency of Elevated ACT Levels in Patients With Bladder Cancers at Various T Categories

	Number	*Abnormals* *≥0.75 g/l*
Controls + T free	143	2 (1.4%)
T1 +ve	28	1 (3.6%)
T2 +ve	13	1 (7.7%)
T1 + T2 +ve	41	2 (4.9%)
T3 +ve	31	18 (58.1%)
T4 +ve	81	50 (61.7%)

Table 6 The Frequency of Elevated CRP Levels in Patients With Bladder Cancers at Various T Categories

	Number	*Abnormals* ≥ 12 *mg/l*
Controls + T free	486	18 (3.7%)
T1 +ve	161	20 (12.4%)
T2 +ve	66	9 (13.6%)
T1 + T2 +ve	227	29 (12.8%)
T3 +ve	62	28 (45.2%)
T4 +ve	101	70 (69.3%)

Higher category disease is associated with a greater proportion of cases in which abnormalities are seen in more than one protein. Abnormalities of both AGP and CRP were present in only 0.4% of the control and tumour-free patients, but in 60% of patients with advanced disease (Table 7).

Table 8 presents the relatively small number of figures from cases in which all 3 proteins have been measured. There was no case in which all 3 proteins were abnormal in a tumour-free patient. Multiple abnormalities were found in 65% of patients with T3 or T4 tumours.

Discussion

The ideal biochemical marker of cancer would be recoverable from patients with the disease and absent from those without it. Many tumours produce such substances and in some types of tumour they are sufficiently specific to have an established place in clinical management, especially in the early detection of recurrence at a time when systemic chemotherapy can be most effectively used. Other tumours, and cancer of the bladder appears to be one of these, have not yet been shown to produce markers which have clinical value (Turner *et al.*, 1977). Diagnostic elevation of plasma CEA, for example, occurs infrequently in carcinoma of the bladder, though when the level is raised it suggests the presence of an invasive tumour (Turner *et al.*, 1977) or metastasis (Hall *et al.*, 1973). When tumours do not produce specific markers themselves, biochemical surveillance has to be directed towards substances produced by the host in response to their presence. The APRPs change in a non-specific manner in response to injury, infection or tissue necrosis. It remains to be established whether the changes seen in advancing carcinoma

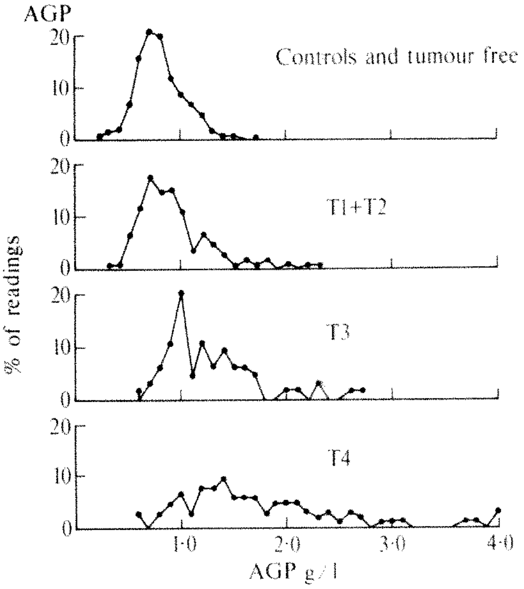

Fig. 2 The distribution of AGP values obtained from patients with bladder carcinoma at different T categories.

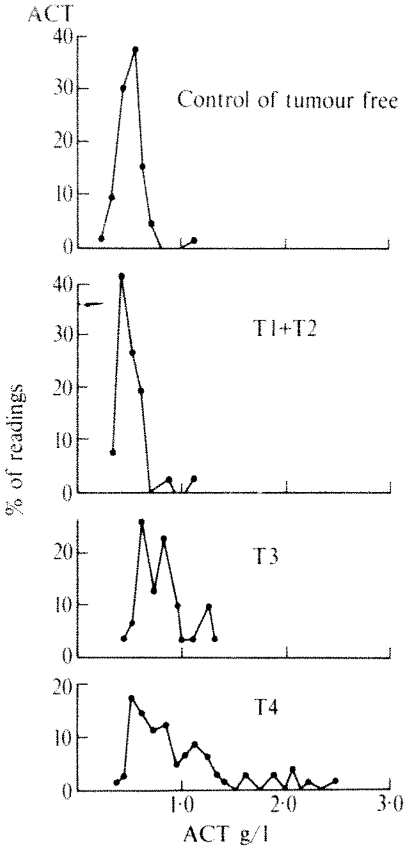

Fig. 3 The distribution of ACT values obtained from patients with bladder carcinoma at different T categories.

Table 7 The Frequency With Which Serum Levels of Either AGP or CRP, or Both, Are Elevated in Patients With Bladder Cancer at Different T Categories

	Number	*Normal*	*Only one abnormal*	*Both abnormal*
T free + controls	487	454 (93.2%)	31 (6.4%)	2 (0.4%)
T1 +ve and T2 +ve	217	167 (77.0%)	35 (16.1%)	15 (6.9%)
T3 +ve	60	22 (36.7%)	11 (18.3%)	27 (45.0%)
T4 +ve	100	18 (18.0%)	21 (21.0%)	61 (61.0%)

Table 8 The Frequency With Which Serum Levels of AGP, ACT or CRP (Alone or in Combination) Are Elevated in Patients With Bladder Cancers at Different T Categories

	Number	*Normal*	*Only one abnormality*	*Two or three abnormalities*
T free + controls	141	131 (92.9%)	9 (6.4%)	1 (0.7%)
T1 +ve and T2 +ve	43	35 (81.4%)	7 (16.3%)	1 (2.3%)
T3 +ve	35	7 (20.0%)	6 (17.1%)	22 (62.9%)
T4 +ve	78	11 (14.1%)	14 (17.9%)	53 (67.9%)

of the bladder are due to these stimuli or are a specific response to the presence of bladder carcinoma cells.

This investigation was aimed at aiding our selection of APRPs for a possible array to be used in the long-term monitoring of invasive bladder cancer. AGP and ACT appear to have the advantage of a "near-normal" distribution and are without the phenotypic variations of HPT and AT. CRP presents a different type of APRP as it is normally at a low level. Caution is required in interpreting elevated levels of this protein, as the rate of change is rapid. The blood level can be expected to reach 100 to 200 mg/l within 24 h of surgery, usually descending by 72 h, though in patients in whom the post-operative period is complicated the CRP may rise again or remain at an elevated level for several days (Fisher *et al.*, 1976). Although the main site of synthesis of CRP, AGP and ACT is the liver, there is recent evidence that AGP can be synthesised by leukocytes (Gahmberg and Andersson, 1978), but as yet we have no evidence as to whether there is any abnormality of production of AGP by leukocytes in patients with bladder cancer.

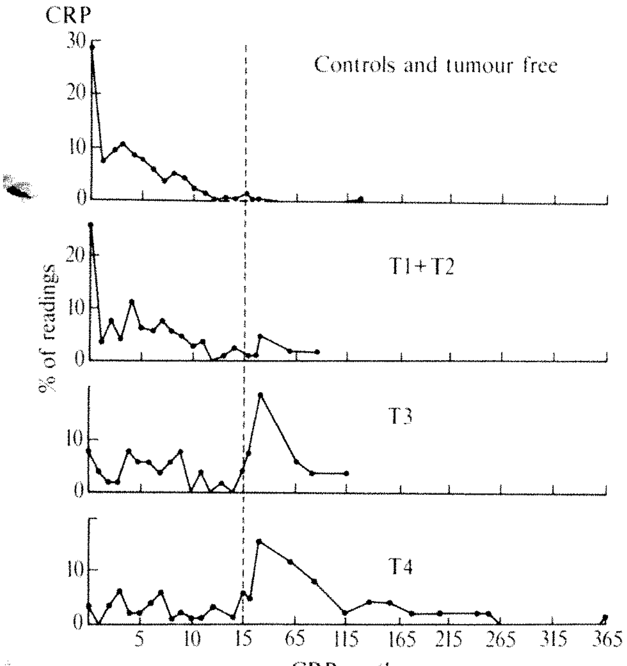

Fig. 4 The distribution of CRP values obtained from patients with bladder carcinoma at different T categories.

Two control populations have been examined—patients with urological conditions other than cancer of the bladder of similar age to the cancer group, and patients who have been treated for cancer of the bladder but have no sign of the disease at the time of examination. It is of course possible that some of the latter group are harbouring occult metastases, but the figures from the 2 populations cannot be separated statistically. As the tumour-free bladder carcinoma patients appear to match the control population they form a useful group against which to compare the bladder carcinoma patients in whom active tumour is present.

The data presented in this paper make it clear that changes in one protein are generally accompanied by changes in the others. Statistical correlations between them are highly significant, and abnormalities in a range of proteins are unlikely to occur in patients who are free of tumour. Although multiple serum protein abnormalities are strongly suggestive of advanced disease, the changes are not sufficiently specific for the APRP levels to act as diagnostic screening aids, especially in a disease where cystoscopy is reliable and relatively easy. The changes are insufficiently marked in low category disease where, in any case, cystoscopy offers the chance of treating recurrences, and in advanced disease the diagnosis is usually obvious from simple clinical examination.

The presence of abnormalities of more than one of the proteins is distinctly unusual in early disease. AGP and CRP were both abnormal in only 0.4% of 454 measurements on subjects who had no evidence of active tumour. This contrasts with the presence of abnormalities in both proteins in 61% of T4 cases. The difference is even more marked when all 3 proteins are taken into account, although the numbers are smaller. Table 8 makes it clear that only 1 of the 141 tumour-free subjects in whom all 3 proteins were measured showed multiple abnormalities, whereas there were at least 2 proteins abnormal in 65% of T3 and T4 cases. It is clear that where more than one abnormality is seen there must be a strong suspicion that the bladder cancer is not localised to the superficial layers of the bladder wall.

The APRP levels were normal in approximately 40% of patients even in the presence of advanced disease. Little information is at present available about the half-life of these proteins in seriously ill patients, although it is now thought that the loss of sialic acid from the glycoproteins, such as AGP, causes them to be removed very rapidly from the circulation (Clamp, 1975). The level in the blood represents a balance between the rates of hepatic production and metabolic destruction, and it seems unlikely that a measurement of the level in the blood in such a dynamic situation would demonstrate abnormalities in every case.

Diagnostic screening is not the only use for biochemical markers. Their value in the early warning of recurrence or metastasis has been demonstrated in several tumours. CEA in colorectal cancer and AFP in testicular teratomas are examples. In bladder carcinoma APRP measurements have a possible role to play both in the screening of patients with apparently localised disease for unsuspected metastases and in monitoring the response to therapy.

APRPs have no place in the diagnostic screening of bladder cancer as the rate of abnormality in early disease is very low, and the rate of abnormalities of more than one protein approaches zero, but multiple abnormalities are commonly seen in advanced disease. It is suggested that APRP measurements may have a place in monitoring the progress of the disease with radiotherapy or chemotherapy, and in the early detection of progression or metastasis.

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Weight Estimation of Benign Prostatic Adenoma with Urethral Pressure Profile

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Summary—An estimation of the weight of the benign prostatic adenoma by quantitative analysis of the urethral pressure profile has been correlated with the surgically removed specimen in 23 patients. It has been found that the length of the continence zone can be used as an index of prostatic weight. After operation the length of the continence zone fell into the normal range of the age matched controls.

It is not uncommon to find, at open operation, that the enucleated prostatic adenoma is smaller than anticipated. Thus the surgeon is aware that the size of the adenoma frequently bears little relationship to the severity of the symptoms and, in borderline cases, a full urodynamic assessment may be necessary.

The size of the prostate has been estimated by various methods including digital examination, cystourethrography (Peirson and Wilson, 1941; Nelson, 1948; Thumann, 1951), prostatography (Sugiura and Hasegawa, 1969), and ultrasonotomography (Watanabe *et al.*, 1975a). The urethral pressure profile (Brown and Wickham, 1969) has been shown to be a valuable clinical measurement in the study of the function of the lower urinary tract (Gleason *et al.*, 1974; Abrams, 1976).

An attempt has been made to correlate the measured size of the prostatic gland with 3 measurements obtained from the urethral pressure profile. In addition, the urethral pressure profiles before and after prostatectomy have been compared with those of age matched and younger controls.

Patients and Methods

Twenty-three patients aged from 56 to 75 (68 ± 6) undergoing prostatectomy were studied, operation being by the retropubic route in 19 cases and the transvesical route in 4. The enucleated adenomas weighed 11 to 85 g (37 ± 22).

The urethral pressures were measured using a 10 Fr Nelaton catheter graduated at 2.5 cm with 4 small holes 5 cm from the end. The catheter was withdrawn at a rate of 30 mm/min and water infused at a rate of 2.5 ml/min (Fig. 1). A recording was made on a heat-writing 2 channel electric recorder (RM-20, Nihonkoden Co.) via a pressure transducer. Three chart speeds were employed: 10 mm/min, 20 mm/min and 50 mm/min (Fig. 2). The recording chart was run fast at 50 mm/min to allow detailed curve analysis. Pressure rise and fall were easier to assess at 50 mm/min. Patients were studied in either a supine or lithotomy position with their bladder empty. Drugs which might affect the urethral function were restricted prior to testing. A single assessment was performed in the majority of patients as measurement error was found to be within 10% on repeated studies.

Three measurements were made: (i) length of

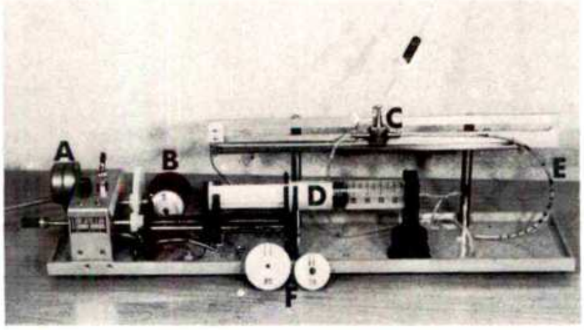

Fig. 1 The urethral pressure profilometer (Kondo, 1978). A synchronous motor (A) drives 2 gear-wheels. One turns a pulley (B) to withdraw a catheter (E). The other pushes a 50 ml syringe (D). Pressure change is sent through the 3-way connector (C) to a transducer. Optional pulleys (F) are provided.

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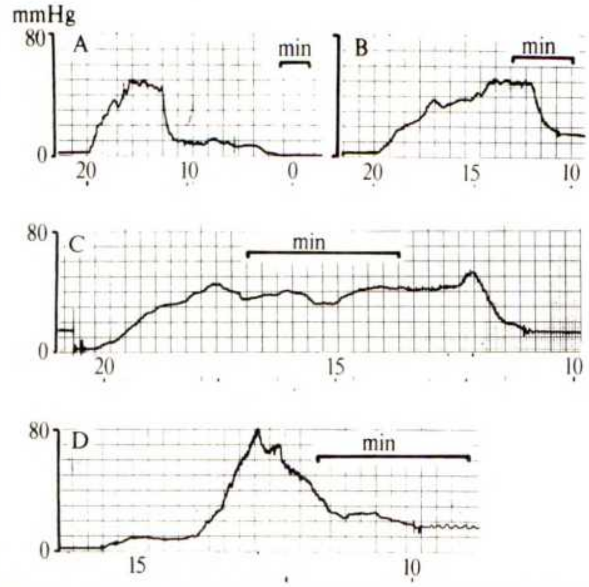

Fig. 2 Difference of urethral pressure profile with 3 different chart speeds recorded on the same patient with benign prostatic hypertrophy (A: 10 mm/min, B: 20 mm/min, C: 50 mm/min). Prostatic gland weighed 85 g. D: A healthy man, 28 years of age, is illustrated in comparison (50 mm/min). Note the short length of continence zone. Numbers below the figure indicate the distance from the external orifice. Catheter was withdrawn at 30 mm/min.

continence zone in millimetres (Fig. 3A), *i.e.* the distance between the bladder neck and the maximum pressure point at the external urethral sphincter, (ii) the maximum urethral pressure in millimetres of mercury (Fig. 3B), and (iii) the area of the continence zone (Fig. 3C) being defined by the base line, vertical line to maximum urethral pressure point and the curve described by the profile to that point. The length of the continence zone was calculated by hand; the area of the continence zone was measured by planimetry using an arbitrary value, where the full range of recording chart (40 mm) was calibrated as 80 mm of mercury (108 cm of water). These 3 measurements were correlated with the weight of the prostatic adenoma removed at operation.

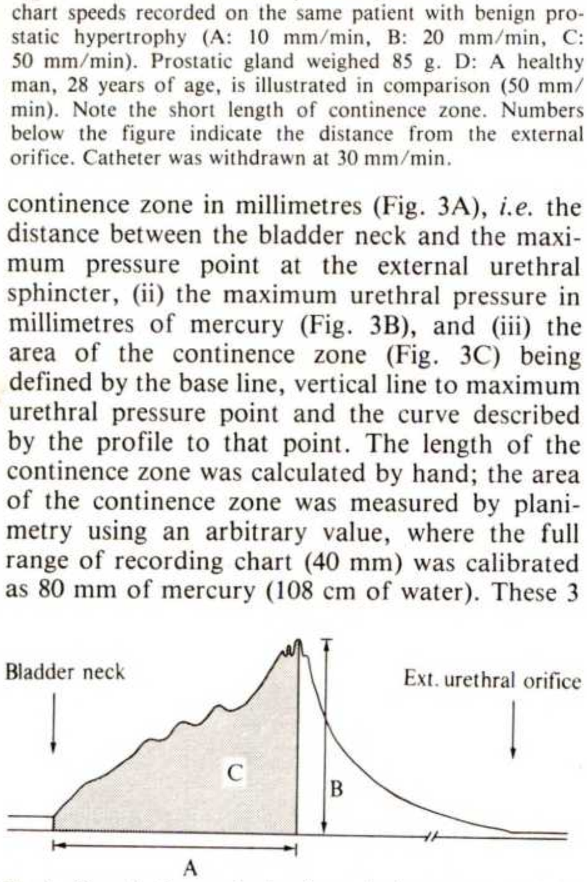

Fig. 3 Quantitative analysis of urethral pressure profile. A: Length of continence zone. B: Maximum urethral pressure. C: Area of continence zone.

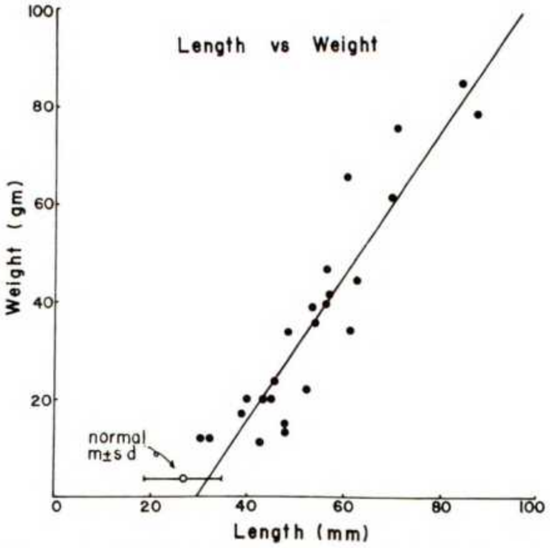

Fig. 4 A significant correlation between the length of continence zone and the weight ($P<0.01$). Normal value found in young controls is 27 ± 8 mm (mean ± standard deviation).

A comparison between the pre-operative and post-operative length and height of the profiles was made as well as an assessment against age matched and younger controls. Fifteen post-prostatectomy patients were studied 2 to 3 weeks after operation. Their ages ranged from 61 to 77 (69 ± 4). The age matched controls were between 55 and 75 years of age (65 ± 6). They consisted of 20 patients who had had no micturition disturbances and no prostatic enlargement on digital examination. Twelve younger patients with no known urinary difficulties acted as controls. Their ages ranged from 20 to 45 (34 ± 9).

Results

(1) Length of continence zone versus weight of adenoma (Fig. 4). The correlation between these 2 values was statistically significant ($P<0.01$). The regression line was calculated as:

$$Y = 1.5X - 45.2 \quad (1)$$

where Y represented the weight in g and X the length in mm.

(2) Value of the maximum urethral pressure versus weight of adenoma (Fig. 5).

No statistical significance was proved between these 2 measurements ($P>0.05$). The regression line was:

$$Y = -0.03X + 39.03 \quad (2)$$

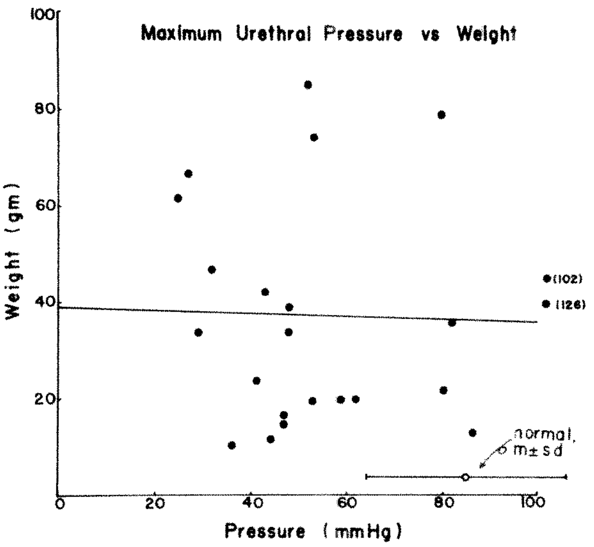

Fig. 5 A non-significant correlation between the maximum urethral pressure and the weight ($P>0.05$). Normal value found in young controls is 85 ± 21 mmHg (mean ± standard deviation).

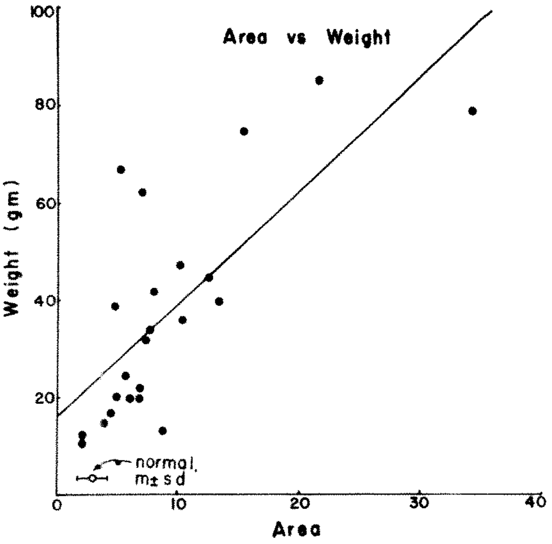

Fig. 6 A significant correlation between the area of continence zone and the weight ($P<0.01$). Normal value found in young controls is 3.6 ± 1.3 in an arbitrary value (mean ± standard deviation).

where Y was the weight and X the pressure in mmHg.

(3) Area of continence zone versus weight of adenoma (Fig. 6).

There was a statistically significant correlation between these 2 values ($P<0.01$). The regression line was:

$$Y = 2.3X + 16.6 \qquad (3)$$

where Y indicated the weight and X the area of continence zone in the arbitrary value.

(4) The length of continence zone and the maximum urethral pressure among 4 groups (Table).

There was a significant difference between the length of the continence zone in the prostatic hypertrophy group and the post-prostatectomy group. A similar significant difference was found between the prostatic hypertrophy group and age matched controls; however, there was no significant difference between the post-prostatectomy result and the length of the continence zone in age matched controls. There was also no significant difference between the 2 control groups.

Comparing the differences between the maximum urethral pressure measurements, a significant difference was found between age matched controls and the post-prostatectomy group as well as between the age matched controls and younger controls. No significant difference was found between the pre-operative and post-operative maximum pressure. Similarly, no significant difference was found between the prostatic hypertrophy group before operation and age matched controls.

Discussion

If the prostatic gland were a sphere the volume would be a direct function of the radius to the third power; this, however, is not the case. The length of the continence zone has been shown in this series to correlate well with the weight of the prostate gland. The continence line has been defined as the point at which the direction of water flow on a pressure profile measurement changes from an inward direction to an outward direction; this is the same point as the maximum urethral pressure. The area between the continence line and the bladder neck has been defined as the continence zone (Gleason *et al.*, 1974). The area of the continence zone has been shown to correlate with the weight of the enucleated gland, but the problem with this measurement is that it requires skill in planimetry and cannot be performed as a routine procedure. No correlation was found between the maximum urethral pressure and the weight of the adenoma.

It is of interest to note that the length of the continence zone was significantly reduced from 55 to 16 mm of mercury on average after prostatectomy. The post-operative value then fell into the range of age matched controls. This observation verifies the relationship between the

Table Comparison of the Length of Continence Zone and the Maximum Urethral Pressure Among 4 Groups

	Prostatic hypertrophy patients	*Post-prostatectomy patients*	*Age matched controls*	*Young controls*
		S^1		
Length of continence zone (mm)	55 (14)	16 (5)	25 (9)	27 (8)
	S^1	NS^1	NS^1	
		NS^2		
Maximum urethral pressure (mmHg)	57 (25)	43 (15)	69 (20)	85 (21)
	NS^1	S^1	S^2	
Age	68 (6)	69 (4)	65 (6)	34 (9)
No. of cases	23	15	20	12

Numbers in parentheses indicate standard deviation. S^1 stands for statistically significant ($P<0.01$), S^2 statistically significant ($P<0.05$), NS^1 not statistically significant ($P>0.1$), and NS^2 not statistically significant ($P>0.05$).

length of continence zone and the weight of prostatic adenoma. When measured 2 to 3 weeks after operation, the maximum urethral pressure in the post-prostatectomy patient was significantly lower than that of the age matched controls. The decrease in value at this stage is probably only transitory and will be elevated into the normal range when complete urinary continence is re-established. The maximum urethral pressure of the age matched controls was significantly lower than that of the younger controls. This confirms the previous finding that the maximum urethral pressure is age related (Edwards and Malvern, 1974).

The size of the prostatic adenoma is one of the main factors used in establishing the diagnosis of prostatism. If the gland is small, an alternative cause for the symptoms of prostatism must be sought and this will include local dysfunction such as bladder neck contracture and systemic dysfunction such as diabetes mellitus and neurogenic bladder.

A poor correlation between the length of the continence zone and the prostatic weight could occur in the following instances: a subvesical lobe protruding into the bladder, a thick surgical capsule, and a disparity in size between the lateral lobes.

The value of the urethral pressure profile measurement for the bladder outflow obstruction was demonstrated by Abrams (1976). He showed that the prostatic length had a high correlation with urethral resistance and age, and that the prostatic peak occurred in 41% of patients over 45 years of age with obstruction. However, we rarely encountered the prostatic peak in this present study and can offer no explanation for this divergence. A simple equation devised by Thumann (1951) for the estimation of prostatic weight involves the difficult measurement of the horizontal diameter of the gland using the cysto-urethrogram. A more refined formula devised by Masuda (1954) is also not practical because of its complexity. Transrectal ultrasonography (Watanabe *et al.*, 1975a) predicts the prostatic weight accurately but it is a complicated procedure and the calculation requires tomographic cuts to be taken at 5 mm intervals (Watanabe *et al.*, 1975b). Since the urethral pressure profile is easy to perform it can be used to evaluate the effectiveness of sphincterotomy, transurethral resection of prostate, bladder neck resections and internal urethrotomies.

This study shows that the length of the continence zone is significantly related to the weight of the enucleated adenoma.

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The Effect of Prostatectomy on Urodynamic Parameters

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Summary—Sixty per cent of men subjected to prostatectomy had unstable bladders. It was found that this was related to the presence of either an indwelling catheter or obstruction, but had little influence on the result of prostatectomy. The functional urethral pressure profile length did not correlate with the size of the prostate gland. Shortening of the prostatic plateau was always found, but the extent to which the plateau was reduced did not correlate with urine flow rates.

Recently there has been renewed interest in the use of drugs and procedures such as bladder neck incision to overcome outflow obstruction in males (Turner-Warwick *et al.*, 1973; Caine *et al.*, 1976). This has stemmed from an increasing knowledge of the factors involved in outflow obstruction. However, the efficacy and relative safety of either transurethral resection or open prostatectomy make it necessary for any new technique to have substantial advantages before it is likely to supplant these well established methods of overcoming outflow obstruction. A major problem associated with the introduction or development of any new technique has been the inability to define what is the minimum required to overcome permanently outflow obstruction caused by the prostate. This has been exemplified by our failure to explain why a prostate of a particular size can cause obstruction, whereas one of identical size produces no urinary symptoms whatsoever. The present studies were carried out in an attempt to provide more information about what happens to the bladder neck and proximal urethra at prostatectomy.

Materials and Methods

Patients who were to undergo prostatectomy had urethral pressure profiles, cystometry and flow rates performed prior to operation. In all instances the decision to perform prostatectomy, which was based on the clinical and intravenous urographic findings, had been made before the urodynamic studies were performed. Sixty-five men were studied, 62 (95%) of whom had a transurethral resection of the prostate and the remaining 3 (5%) a retropubic prostatectomy. Informed consent was obtained from all patients and similar studies were repeated between 3 and 6 months after prostatectomy. Any patient who was found to have a urinary tract infection was excluded from the study.

Urethral pressure profiles were performed using the method described by Harrison and Constable (1970), with a constant infusion rate of 10 ml/min. Cystometry was performed with the patient supine (in a standard manner), using gravity filling with the reservoir 70 cm above the symphysis pubis. The bladder, rectal, and bladder minus rectal pressures were measured and it was the subtracted pressure that was used to diagnose detrusor instability. Voiding pressures were not used in this study. It was found that elderly men often had difficulty voiding, even with a fine urethral catheter *in situ* and, as we wished to compare peak flow rates, voiding pressures were not determined. Urine flow rates were measured using a Disa flow meter.

Results

The age distribution of the men studied is shown in Figure 1. Few were under the age of 60 and the majority were in their seventh or eighth decades. Of the 65 who were studied initially, 5 were diagnosed pre-operatively as having carcinoma, and these men were not subjected to follow-up studies as no attempt was made to achieve maximal clearance of the prostate, but only to provide a

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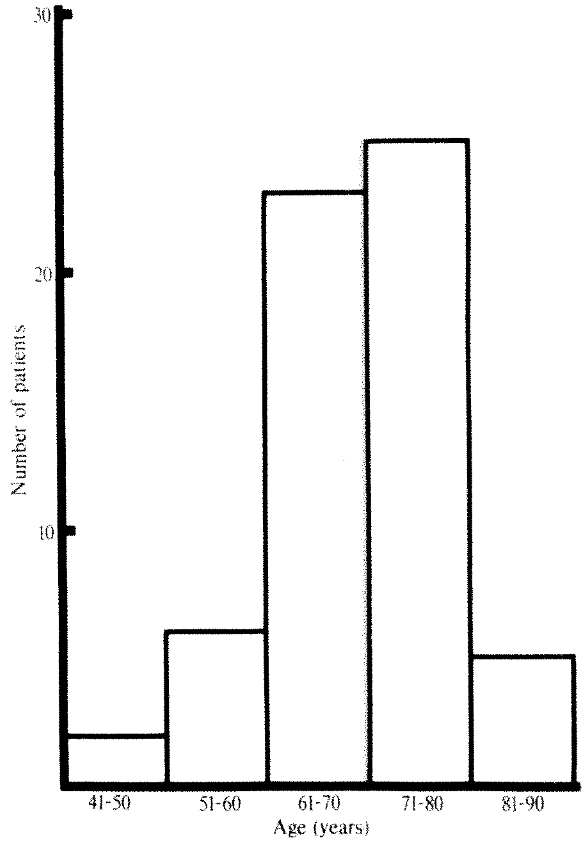

Fig. 1 Age distribution.

channel. Of the remaining 60, 20 did not undergo repeat assessment and the reasons are shown in Table 1.

Thus 40 men had studies before and after prostatectomy.

The indications for operation in the 60 with benign hyperplasia are shown in Table 2. Approximately one-half had acute retention and the remainder were subjected to surgery because of their symptoms and intravenous urogram findings. Nocturia, frequency and poor stream were the principal symptoms, and nearly 90% of patients had at least one of these symptoms.

Table 1 Failed to Have Repeat Study

Reason	*No.*
Refused	8
Too ill (patient's assessment)	4
Recent cerebrovascular accident	2
Died	2
Moved away	2
Technical difficulties	2
Total	20

Table 2 Indications for Operation

Acute retention	25	41.7%
Chronic retention	3	5.0%
Symptoms of obstruction	32	53.3%

Only 40% of these men (Table 3) had normal cystometrograms despite the fact that the studies were performed supine. Of the remainder, 72% had a small capacity unstable bladder; values below 250 ml were arbitrarily taken as the volumes that separated a small capacity unstable bladder from what was considered to be a normal capacity unstable bladder. A sudden rise in pressure of a minimum of 15 cm of water was considered to indicate detrusor instability. Each group was further subdivided (Table 4). In those with a normal cystometrogram, the majority presented because of symptoms. On the other hand, in those with a small capacity unstable bladder, the proportion was reversed with the majority presenting with acute retention of urine and with an indwelling catheter at the time of the initial study. Moreover, the majority of the men with normal capacity unstable bladders were not in retention. Three men were considered to have chronic retention. As they were divided equally between the 3 groups (Table 4), their inclusion had no effect on the subdivision of patients.

From the follow-up studies it can be seen (Table 5) that those cystometrograms considered to be normal pre-operatively were not altered. However, in those with unstable bladders, 18 out of 22 (82%) had normal studies 3 months after prostatectomy. Of the 4 who had persistently unstable bladders, 2 had had cerebrovascular accidents 12 months pre-operatively and still had other neurological abnormalities.

When examining the urethral pressure profiles, 2 measurements were taken: the total length and

Table 3 Cystometrogram

Normal	24/60	40.0%	
Abnormal (Vol < 250 ml)	26/60	43.3%	60.0%
Abnormal (Vol > 250 ml)	10/60	16.7%	

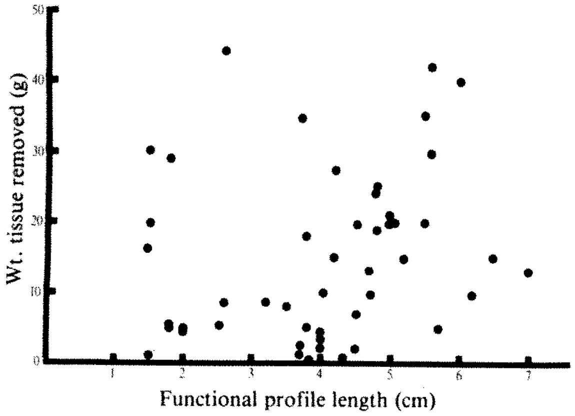

Fig. 2 Functional length v. weight.

the functional length. The total length was measured from the first rise in pressure as the catheter left the bladder to the point where the peak ended. The functional length, which was the same as that measured by Abrams (1976), was taken from the first rise in pressure to the point which represented the maximum urethral closure pressure.

In Figure 2 the weight of prostatic tissue removed has been plotted against the functional profile length. There was no significant correlation between the amount of tissue removed and profile length. A similar lack of correlation was found if the total length was used. When the post-prostatectomy profile lengths were compared with the pre-operative studies (Fig. 3), a significant reduction in length was observed ($P<0.001$, paired t-test). However, no correlation (Fig. 4) could be found between the extent of the reduction in profile length and post-operative urine flow rates. Similarly, no correlation could be found between changes in the area under the profile curve and urine flow rates, or between the pre-operative flow rates and the height of the prostatic plateau. The age of the patient at the time of operation did not appear to have any influence on the peak urethral closure pressure. Following prostatectomy it was found that there was no significant change in the peak urethral pressure. Finally, it can be seen (Table 6) that the mean flow rate of men who had prostatectomy because of symptoms showed a 2.5-fold increase. An almost identical improvement in flow rate was observed in those patients who had the operation because of retention, indicating that the operation *per se* had been effective.

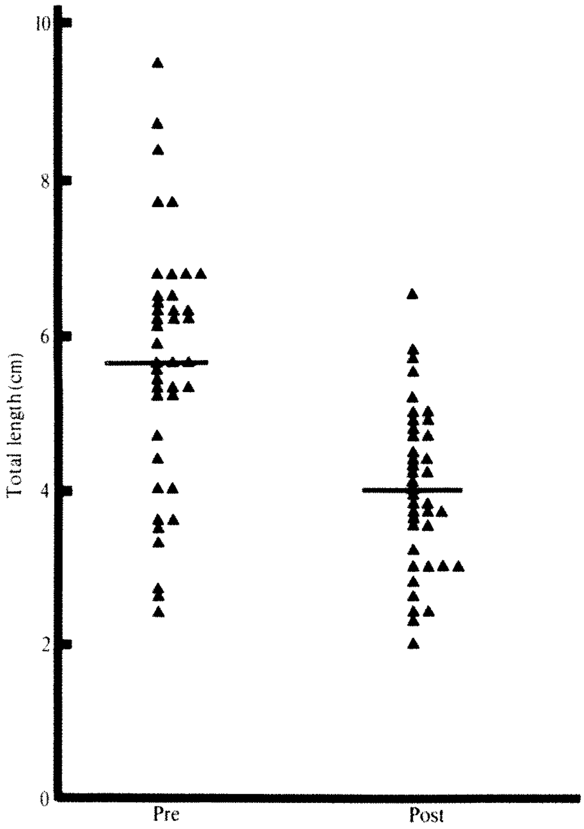

Fig. 3 Effect of prostatectomy on profile length.

Discussion

From this study it was evident that a high proportion of men subjected to prostatectomy had unstable bladders. Hebjørn *et al.* (1976) have reported a similar high incidence of detrusor instability. In this study, it would seem that the presence of an indwelling catheter or the recent decompression of the bladder had resulted in an artificially high incidence of detrusor instability. In the men with an unstable, but normal capacity bladder, most of them required surgery because of symptoms, suggesting a significant incidence

Table 4 Cystometrogram

Normal	Retention A(6), C(1) Symptoms	7/24 17/24	29.2% 70.8%
Abnormal (Vol<250 ml)	Retention A(17), C(1) Symptoms	18/26 8/26	69.2% 30.8%
Abnormal (Vol>250 ml)	Retention A(2), C(1) Symptoms	3/10 7/10	30.0% 70.0%

A = Acute retention
B = Chronic retention

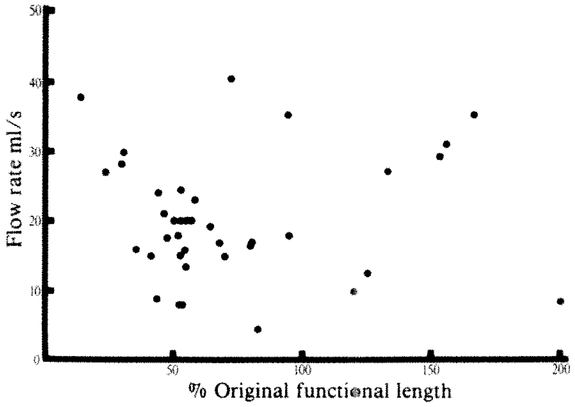

Fig. 4 Change in functional length and flow.

Table 6 Urinary Flow Rate and Prostatectomy

	Pre	*Post*
Symptoms (20)	8.5 ± 6.4 ml/s	20.2 ± 8.0 ml/s
Retention (15)	—	20.1 ± 9.9 ml/s

of instability in this group which was not catheter-related. Only 4 (18%) of the men studied had persistently unstable bladders. In 2 of these a previous dense cerebrovascular accident appeared to be a likely contributing factor. No obvious explanation could be found for the persistent instability in the other 2. They were both satisfied with the result and in each case had a flow rate in excess of 20 ml/s. Their pre-operative symptoms were unremarkable and, while it was tempting to repeat the studies after a further 6 months, it was not felt justified in a patient well satisfied with the outcome of his operation. Therefore, although detrusor instability was a relatively common finding in men with acute or chronic retention, or severe symptoms of outflow obstruction, it settled rapidly after prostatectomy and had little effect on the final result of the operation. As this instability appeared to settle soon after surgery in most instances, it would seem that its persistence should raise the suspicion that inadequate removal of the prostate has occurred.

Prostatectomy resulted in significant shortening of the pressure profile. This is in agreement with the findings of Andersen *et al.* (1976), as is the observation that the amount of tissue removed does not correlate with the length of the profile. It is perhaps not surprising that no correlation exists between the length of the profile and the amount of tissue removed, as the weight of tissue removed would more accurately reflect the volume of the prostate rather than the length of the gland. Certainly a relatively broad but short prostate is unlikely to correlate well under these circumstances. What was surprising, however, was the relatively inconstant position of the peak pressure and presumably the major functional component of the external sphincter. For example, in 23 men in whom 10 g of tissue or less was removed, the position of the peak of the profile ranged from 1.5 to 6.2 cm from the bladder neck. Why the position of the peak pressure was so variable from one individual to another is not clear. It is not influenced by the size of the prostate, as might have been expected. However, this variability in position and, in some instances, the close proximity of the external sphincter mechanism to the prostate gland, may explain why some patients have a degree of incontinence after what has been apparently a technically sound operation.

A prostatic plateau was seen in all cases, but definite prostatic peaks as described by Abrams (1976) were not seen. Also, no correlation was found between the age of the patient and the length or the height of the profile. Although the abolition of part of the prostatic plateau occurred in every case, the extent of the change did not correlate with the subsequent flow rates. Men in whom the prostatic plateau appeared to have been abolished completely had flows comparable to those found in men in whom relatively small changes had occurred. It could be argued that as abolition of part of the plateau occurred in all

Table 5 Repeat Cystometrogram > 3 Months

At presentation			*After 3 months*	
		Mean vol ± SD	*Mean vol ± SD*	
Normal	18/40	383 ± 113	447 ± 164	All stable
Abnormal (< 250 ml)	15/40	133 ± 70	365 ± 81	2 unstable
Abnormal (> 250 ml)	7/40	407 ± 134	392 ± 120	2 unstable

cases, the pressure profile is a satisfactory way of indicating what is required to overcome outflow obstruction. However, a better correlation would appear necessary if changes in profile measurements were to be used to predict whether a particular drug or bladder neck incision, for example, would satisfactorily relieve obstruction caused by the prostate.

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We wish to thank Dr Graham Sinclair for allowing us to study patients under his care.

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Human Prostatic Lymphoscintigraphy. A Preliminary Report

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Summary—A simple method for demonstrating prostatic lymphatic drainage by transrectal injection of ^{99m}Tc labelled antimony sulphide colloid into the prostatic capsule has been developed. This technique may be readily applied in clinical practice with obvious potential in the assessment and follow-up of patients with carcinoma of the prostate.

Lymphangiography is now established in the investigation of abnormalities in the external and common iliac lymph nodes. Drainage from the pelvic viscera, in contrast, passes along the internal iliac lymphatics which are not demonstrable by pedal lymphography.

^{99m}Tc antimony sulphide colloid (TASC) injections have been given at various sites to male patients aged 55 years and over during routine cystoscopy. The transrectal site is the only one which has demonstrated lymphatic drainage with sufficient reliability and our results suggest that this is a viable technique for routine investigation of the lymphatics draining prostatic tissue.

Materials and Methods

Twenty-five patients who underwent cystourethroscopic follow-up for superficial bladder tumours consented to have a small dose of antimony sulphide colloid labelled with ^{99m}Tc injected at the end of the procedure while they were still under general anaesthesia. This was chosen as the imaging agent because its radiation dose is considerably less than ^{198}Au and its particle size is also sufficiently small (the manufacturers claim 4 to 12 nm) for it to be drained well by lymphatics. Although different concentrations have been used, our present preparation aimed to achieve a total activity of 15 mCi in the finished volume of 6 ml. In the present technique, 125 μCi (0.05 ml) were injected into 2 sites in the prostatic capsule on either side of the midline, using a Franzen needle *per rectum*.

Scintigraphy was undertaken with a Nuclear Enterprises Mark III gamma camera at 3 h and at 6 h following injection. Both anterior and posterior views of the prostatic region were obtained on Polaroid film and, when lymph node uptake was observed, satisfactory films were produced with 50,000 counts.

Results

Twenty-five patients have been investigated. In the first group, 2 patients were given injections into the prostatic parenchyma transperineally (Table). Activities of about 125 μCi were given in volumes of less than 0.2 ml, one injection on either side of the midline. No successful images of lymph nodes were obtained from these patients.

In the second group, 15 patients received transurethral injections through a 21 gauge needle attached to the end of a 6 FG ureteric catheter introduced and directed through the cystoscope. In 4 patients several small injections (less than

Table Methods for Injecting Radionuclide

Group I (2 patients)	
Transperineal	
Group II (15 patients)	
intraparenchymal	4
Intravesical	11
Superficial trigone	2
Deep trigone	2
Posterior wall	3
Anterior wall	2
Periureteric	2
Group III (1 patient)	
Transabdominal into retropubic space	
Group IV (7 patients)	
Transrectal into prostatic capsule	

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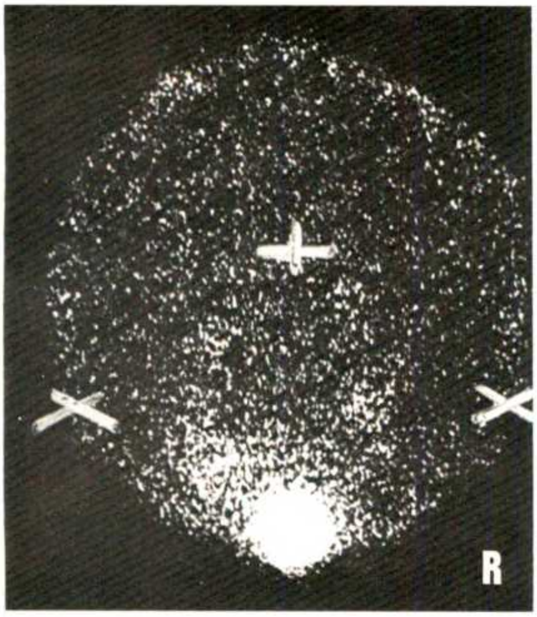


Fig. 1 (J.C.) Lymphatic drainage 3 h following transurethral injection of ^{99m}Tc antimony sulphide colloid into the prostate. The largest area of intensity in all of the scintigrams is the injection site. (The central cross indicates the position of the umbilicus and the lower crosses indicate anterior superior iliac spines.)

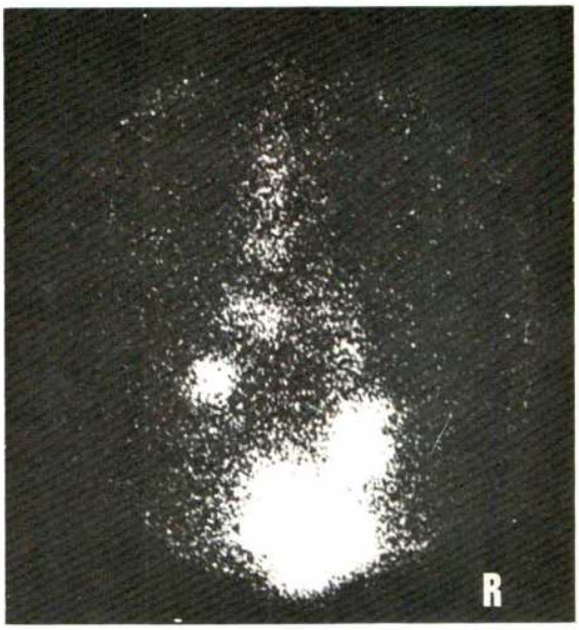


Fig. 2 (S.C.) This scintigram demonstrates the pathway of lymphatic drainage up to and including the para-aortic lymph nodes.

0.1 ml) were made into the prostatic parenchyma but in only one case was lymphatic drainage shown on the scintigram (Fig. 1). The remaining patients in this group underwent intravesical injection: into the superficial trigone in 2 cases, the deep trigone in 2, the posterior wall in 3, the periureteric areas in 2 and into the anterior wall in a further 2 cases. In the third group, one patient only received an injection into the retropubic space by a needle inserted through the anterior abdominal wall. None of these was successful in demonstrating lymph node uptake on the scintigrams.

In the final group, 7 patients were given ^{99m}Tc antimony sulphide colloid by a transrectal injection and in all cases lymph drainage was demonstrated on the scintigram. Figures 2 and 3 show examples of patients investigated by this technique and illustrate patterns which are recognisable as internal iliac lymph nodes. In these cases the colloid was given in 2 small injections into the posteroinferior capsule on either side of the midline. Each injection consisted of up to 125 μCi in a volume of about 0.05 ml. As the illustrations indicate, the lymph node uptake was well defined. In most instances scintigraphy at 6 h following injection showed no improvement over that done at 3 h.

All patients in the final group were given antibiotic cover with benzyl penicillin (1×10^6 units intramuscularly) and lincomycin (0.5 g orally)

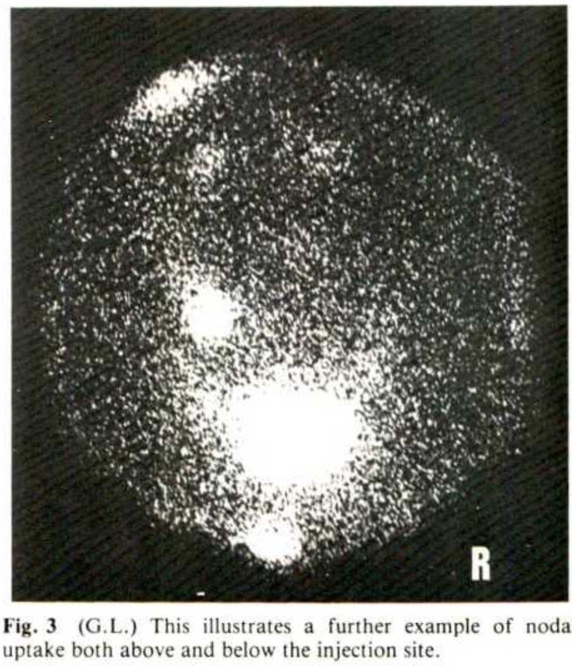


Fig. 3 (G.L.) This illustrates a further example of nodal uptake both above and below the injection site.

with the premedication. Those allergic to penicillin received 0.5 g tetracycline instead. Apart from the first 3 patients, who underwent transrectal injection, all received a 5-day course of cotrimoxazole (1 injection twice daily). Among the 3 exceptions, one patient was asymptomatic but the other 2 developed symptoms of urinary tract infection—one with a positive urine culture.

Discussion

Lymphatic drainage from the prostate gland has not been reliably observed by techniques applicable to routine clinical investigation. Menon *et al.* (1977) injected 1 to 2 mCi ^{198}Au colloid into the prostate gland of the dog through an open bladder and in subsequent scintigraphy were able to demonstrate periprostatic, internal iliac and other nodes. ^{198}Au has the advantage over other materials of a small particle size (3 to 5 nm) but its high radiation dose is a serious limiting factor in the clinical situation.

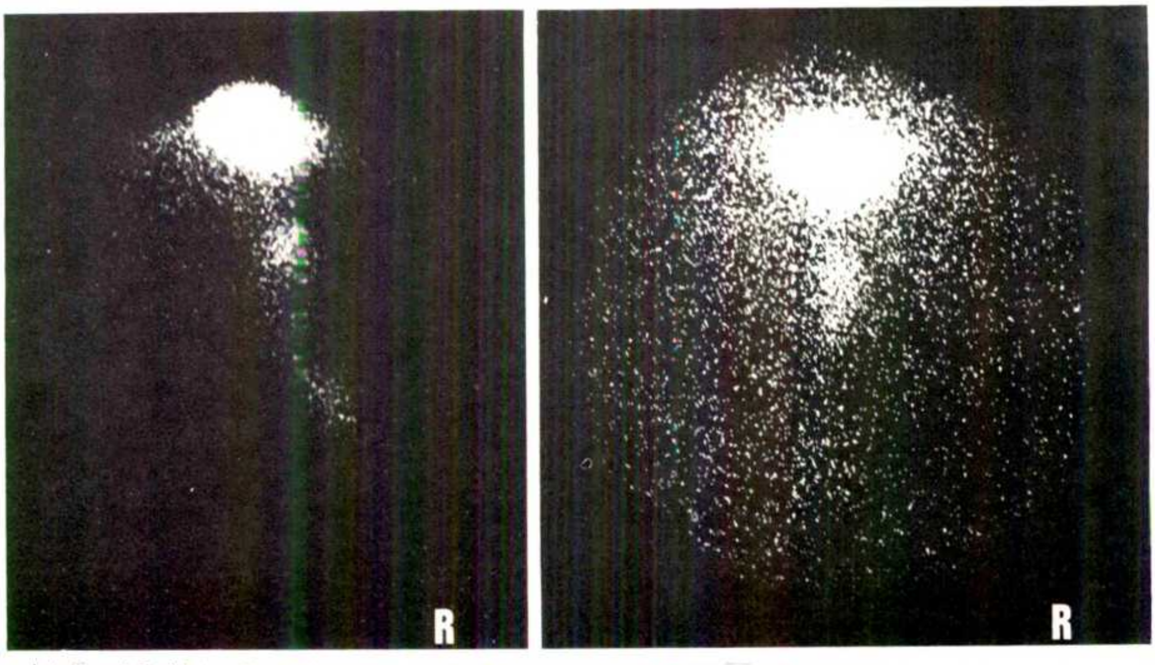
McCullough (1975) injected contrast media into rat prostatic parenchyma and found that no lymphatic vessels could be seen unless spillage into the capsule occurred. His results supported the view that intraprostatic lymphatics may be absent in man and that the prostate may represent an immunologically privileged site.

Whether or not prostatic lymphatics exist in the human has been a matter of speculation for many years. Our results using the transurethral route for injection tend to support the view that parenchymal lymphatics do not exist (Smith, 1966; Rodin *et al.*, 1967; McCullough, 1975). Our success with the transrectal injections would indicate, however, that there may be lymphatics in the capsular area. In the one instance where transurethral injection into the prostate did succeed in demonstrating lymphatic drainage the injection had been made deeply in a small prostate and almost certainly into the capsule.

Figures 4 and 5 show what appears to be the passage of radionuclide into the urethra. Why this should occur is not absolutely clear but it may be that part of the dose spilled into the intraprostatic ductal system and then drained directly into the urethra.

With the transrectal approach, small aliquots of radionuclide were injected into the capsule, avoiding the tendency for isotope to pool and not find its way from the injection site into the lymphatic system (as described by Menon *et al.*, 1977). Possibly this is the reason for the failure of the initial transperineal injections.

The use of ^{99m}Tc antimony sulphide colloid for breast lymphoscintigraphy has been reported in some detail by Ege (1976, 1978) and the success



Figs. 4 (left) **and 5** (right). Show what appears to be the passage of radionuclide into the urethra.

of the technique, which involves subcutaneous injection, is ascribed in some degree to the small uniform particle size. Electron microscopy of a representative sample of the labelled antimony sulphide colloid used in our investigations showed a prevalence of particles ranging in size from 4 to 20 nm, but larger particles up to 40 nm were also present.

The radiation dose to the lymph nodes is very variable and no exact estimate has been made. However, in the event of all of the activity remaining at the injection site and concentrated in a tissue volume of about 1 cm^3, the dose to this region would be about 2.5 rad for an administered activity of 250 μCi of TASC. The same administered activity of ^{198}Au colloid would result in a dose of about 100 rad, emphasising the advantage of using the technetium preparation. A dose of 2.5 rad to this relatively radiation-insensitive region of the body is well within acceptable limits, allowing the technique to be considered for routine clinical investigations of prostatic lymph drainage.

By conventional non-invasive techniques, lymphatic drainage of the prostate cannot be shown in the clinical situation. The limitations of clinical staging in carcinoma of this gland are well recognised and other indirect approaches have been proposed in order to indicate tumour extension more clearly. Among these, the use of ultrasound (Resnick *et al.*, 1978) and vasoseminal vesiculography have been proposed (Beck *et al.*, 1978). Computerised axial tomography is being used more and more frequently but its limitations in demonstrating nodal spread of tumour are considerable (Stewart *et al.*, 1978).

In the present study a very simple technique which has not been used previously has been investigated. Useful scintigrams have been obtained, indicating that lymph nodes can be reliably demonstrated. It remains now for the technique to be applied to the investigation of patients with prostatic carcinoma and to examine the criteria by which normal uptake patterns might be distinguished from abnormal. Only ^{99m}Tc antimony sulphide colloid has so far been used and it is possible that the scintigrams obtained with this material alone may have good diagnostic possibilities. However, we are investigating the possibility that, in combination with other agents, a more reliable sequential study may be devised.

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Ultrastructure of the Normal Human Urethra

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Summary—The normal ultrastructure of the prostatic, bulbar and penile urethra in the human is described. The human urethra contains both exocrine and what appear to be endocrine glands. Further study is in progress to define the nature and role of the secretion from these endocrine glands.

Many pathological conditions affect the human urethra but there is little information on the normal ultrastructure. An electron microscope study of the normal urethra is presented.

Patients and Methods

Patients were selected for the study only after fulfilling all of the following criteria:

1. There was no past history of urethritis or trauma to the urethra (accidental or instrumental).
2. The urine was sterile.
3. Cystourethroscopy showed no sign of cystitis or urethritis.

Six patients whose ages ranged between 45 and 65 years were studied. Four patients were admitted for transurethral resection of the prostate because of symptoms of prostatism, and 2 (aged 45 and 51 years) were admitted for bladder neck incision.

Pentothal was used for induction and Halothane for maintenance of general anaesthesia. Preliminary cystourethroscopy was carried out using a Storz cystourethroscope FG 21. Biopsies were taken from the mid-prostatic, bulbar and penile urethra using Storz biopsy forceps. The 3 separate specimens were immediately placed in 4% glutaraldehyde in 0.1M cacodylate buffer at pH 7.2 to 7.4 at 4°C. All specimens were labelled and sealed in a plastic envelope and placed immediately in a thermos flask with ice cubes surrounding the plastic envelope. Because urethral epithelium appeared to be shed quickly, it was fixed rapidly for electron microscopy. The specimens were left in cold 4% glutaraldehyde for 2 to 6 hours, then washed with cacodylate buffer and fixed with 1% osmium textroxide.

Results

Prostatic urethra

A well formed basal lamina separated the epithelium and the connective tissue in the subepithelial layer.

Epithelium (Figs. 1, 2, 3 and 4). Three cell types—basal, intermediate and superficial—were identified. The *basal* cell type was small and oval with minimal cytoplasm; in some areas the intercellular spaces were wide and in these spaces sheet-like cellular processes were seen. The cytoplasm was darkly stained and contained free ribosomes and rough endoplasmic reticulum. Golgi apparatus and secretory granules were present but not prominent. The nuclei of these basal cells were large, oval with a few shallow indentations, and contained one or more nucleoli. There was a dense band of heterochromatin lining the periphery of the nucleus.

The *superficial* cell type was larger with an abundant cytoplasm which was lighter in colour. Secretory granules, Golgi apparatus, endoplasmic reticulum and mitochondria were easily identified. Along the lumen of the urethra short microvilli and occasionally pinocytic invaginations were seen. The nucleoli were larger, but rarely identified, and the peripheral heterochromatin zone was thin.

The third cell type resembled the basal cell type in morphology but it seemed secretory in function. Some of these cells discharged their secretions in the lumen of the urethra; others were loaded with secretory granules.

In between the epithelial cells sensory nerves, polymorphs or lymphocytes were seen.

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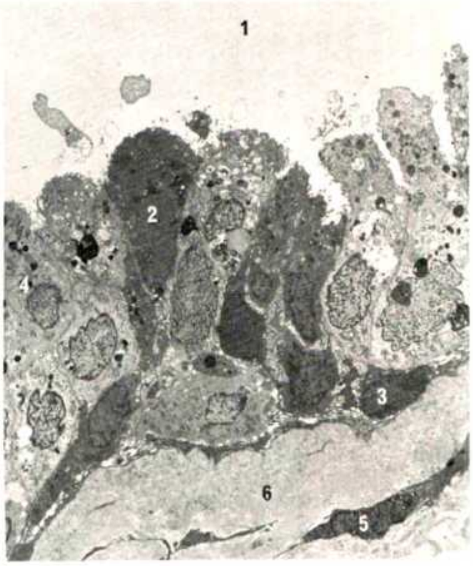

Fig. 1 Normal prostatic urethra: (1) lumen, (2) intermediate cell type, (3) basal cell type, (4) superficial cell type, (5) fibroblasts, (6) collagen fibres in the subepithelial connective tissue. (×3,000).

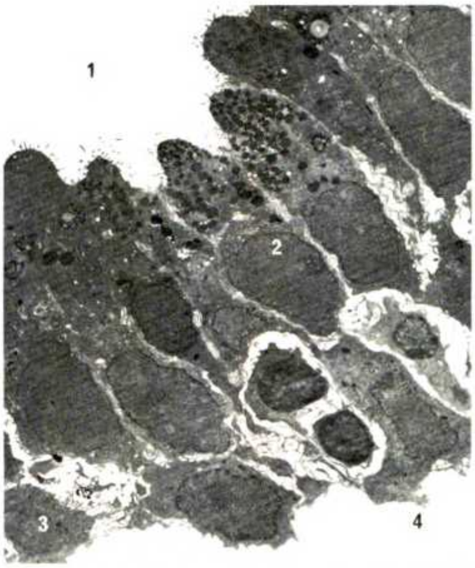

Fig. 2 Normal prostatic urethra: (1) lumen, (2) intermediate cell type, (3) basal cell type, (4) subepithelial connective tissue. (×4,500).

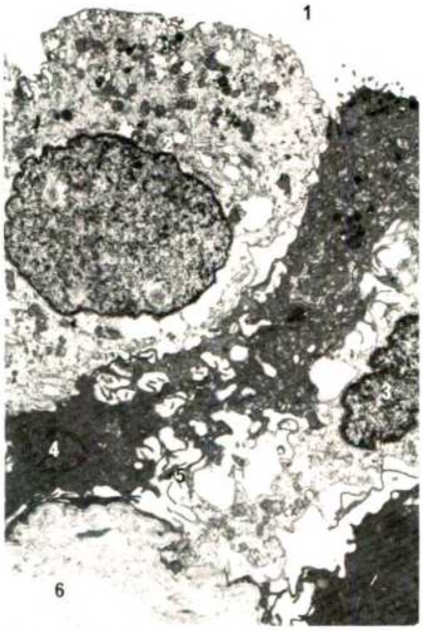

Fig. 3 Normal prostatic urethra: (1) lumen, (2) superficial cell type, (3) intermediate cell type, (4) basal cell type, (5) intercellular cytoplasmic processes, (6) subepithelial connective tissue. (×7,500).

Fig. 4 Normal prostatic urethra: (1) lumen, (2) microvilli, (3) rough endoplasmic reticulum, (4) junctional complex. (×30,000).

The subepithelial layer consisted of a cell-rich connective tissue which represented an intermediate type between loose and dense connective tissue.

Irregularly arranged collagen completely filled the intercellular spaces. An abundance of fibroblasts was seen, and also macrophages and lymphocytes. Myelinated nerve, smooth muscle and exocrine gland-like structures were only occasionally identified.

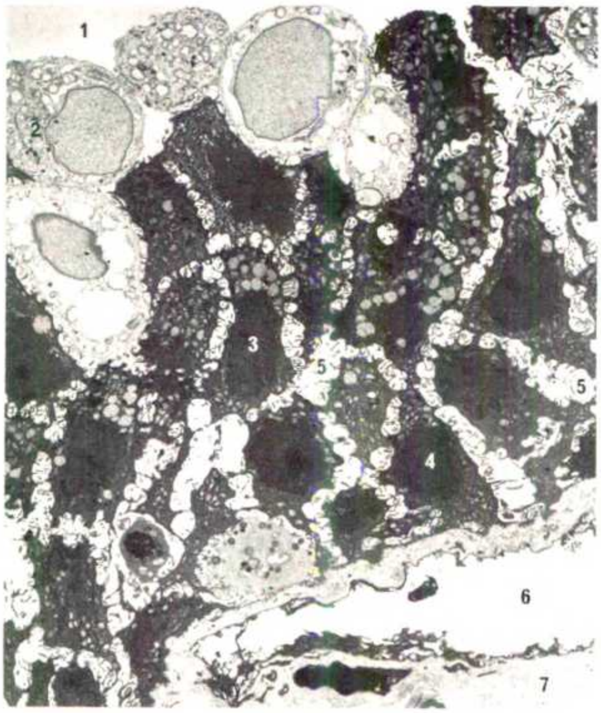

Fig. 5 Normal bulbar urethra: (1) lumen, (2) superficial cell type, (3) intermediate cell type, (4) basal cell type, (5) intercellular cytoplasmic processes, (6) large blood vessel in the subepithelial layer, (7) collagen fibres. (×3,000).

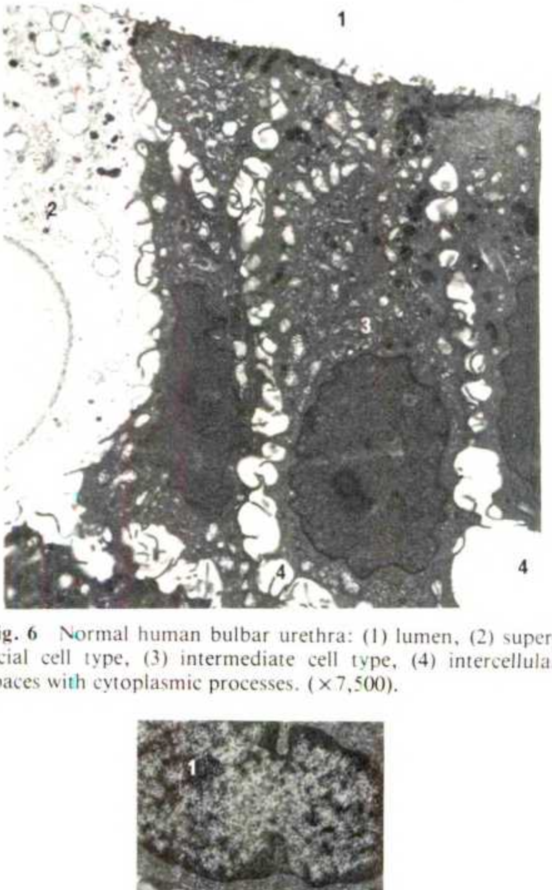

Fig. 6 Normal human bulbar urethra: (1) lumen, (2) superficial cell type, (3) intermediate cell type, (4) intercellular spaces with cytoplasmic processes. (×7,500).

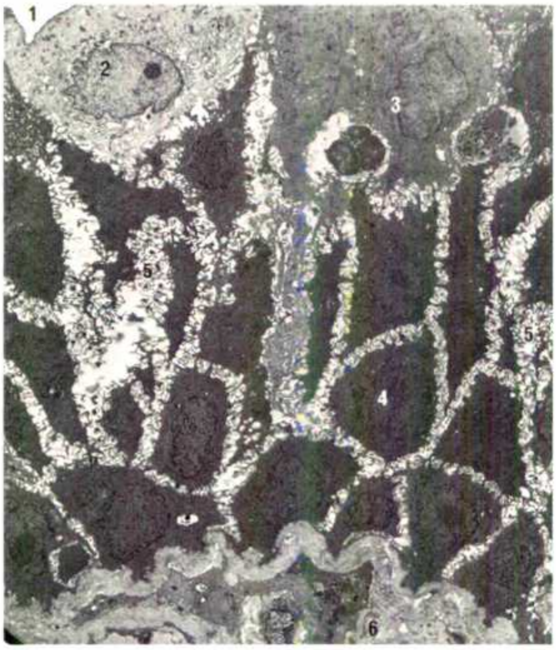

Fig. 7 Normal penile urethra: (1) lumen, (2) superficial cell type, (3) intermediate cell type, (4) basal cell type, (5) intercellular cytoplasmic processes, (6) subepithelial connective tissue. (×3,000).

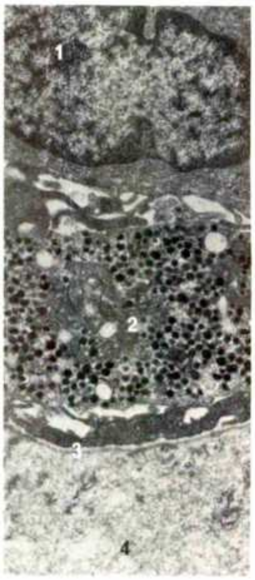

Fig. 8 Normal penile urethra: (1) basal cell type, (2) an endocrine gland (APUD), (3) basal lamina, (4) collagen fibres in the subepithelial connective tissue. (×18,000).

Bulbar and penile urethra (Figs. 5, 6 and 7)

Epithelium. Three cell types were identified. The basal cell type closely resembled the basal cell seen in the prostatic urethra, but the superficial cell type differed slightly. The cells were similar in size to those of the basal cell type and were arranged in 3 or more multiple layers. The intercellular spaces were more apparent and in these spaces there were mainly sheet-like cellular processes. The cytoplasm of the superficial cell type was lighter in colour than the basal cell type. Golgi apparatus or secretory granules were not prominent. Along the urethral lumen short microvilli were seen. The nuclei of these superficial cells were large with many deep indentations; one or occasionally 2 nucleoli were seen. A band of heterochromatin was also seen but was much thinner than that seen in the basal cell type. The third cell type occasionally seen closely resembled a simple branched tubular gland seen in the human cervix.

Between the basal cell types, or resting on the basal lamina, were observed cells, or parts of cells, containing "neurosecretory" granules (Fig. 8). These were considered to be representatives of the Diffuse Endocrine System (Pearse, 1969, 1977) analogous to the diffusely distributed cells of the paraganglia, secretory catechol or other amines and, possibly, active peptides.

The subepithelial layers in the prostatic, bulbar and penile urethra were similar.

Discussion

Notley (1968, 1976) described the electron microscopy of the ureteric epithelium as being composed of 3 cell types—superficial, intermediate and basal. In general terms this may seem similar to the description of the human urethra. A few differences, however, do exist. The intermediate cell type in the urethra is morphologically and functionally different from that in the ureter. The cytoplasm of these cells in the urethra contained large numbers of secretory granules and some of these granules seemed to have discharged their secretion in the urethral lumen.

In between the basal cell type, and rarely in the subepithelial layer of the bulbar and penile urethra, cells containing "neurosecretory" granules were seen. These cells were essentially similar to those described by Pearse (1969, 1977) as members of the APUD series constituting the Diffuse Endocrine System. Work is currently in progress to identify cytochemically the products of these potentially hormone-producing cells, and to establish their role in the human urethra.

In the subepithelial layer, the human urethra resembles the subepithelial layer of the mouse urethra described by Rhodin (1974). In addition, special fibrils were seen in between the abundant collagen fibres; these fibrils looked very similar to the fibrils described by Rowlatt (1969) in the mouse uterus.

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Fracture of the Penis with Laceration of the Urethra

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Summary—Two patients are described with severe injury to the penis sustained during sexual intercourse. The literature is reviewed. A conservative approach to management with suprapubic urinary diversion led to acceptable results.

Fracture of the penis occurs with injury to the erect organ. The fibrous sheath of the corpus cavernosum is torn with haemorrhage, haematoma formation and distortion of the organ. In some cases the tear extends into the corpus spongiosum with laceration of the urethra.

It is an uncommon injury with only 30 cases reported in the American literature up to the present time (Gross *et al.*, 1977). Two cases managed by the author are described.

Case Reports

Case 1. A male aged 43 was having sexual intercourse when his penis slipped out and he came down hard on his partner's pubis. Immediately he felt severe pain in his penis and the erection subsided. Later he had urethral bleeding.

On admission to hospital the penis was grossly deformed by haematoma and the bladder palpable suprapubically. Under anaesthesia a soft catheter was passed into the bladder but then withdrawn and a suprapubic catheter inserted by open surgery. Ten days after surgery the patient was referred to the Urology Service.

A micturating cystourethrogram 3 weeks following injury revealed a stricture at the penoscrotal junction partly occluding the urethra (Fig. 1). The suprapubic catheter was then removed. This stricture was no longer apparent after 2 dilatations. At one year the patient had a good stream, minimal downward bend on erection and was satisfied with the situation. A small firm plaque was palpable in the base of his penis.

Case 2. A male aged 26 injured his penis in similar circumstances to the above. This man heard a crack when the injury occurred.

On admission to hospital he had gross subcutaneous haematoma of the penis and scrotum and profuse urethral bleeding. Using a closed technique a suprapubic catheter was inserted into the full bladder. A firm crepe bandage had to be applied to the penis to control the haemorrhage. A retrograde urethrogram on the seventh day following injury revealed an intact urethra with a small filling defect at the level of the penoscrotal junction (Fig. 2). Satisfactory voiding occurred when the suprapubic catheter was removed on the tenth day.

Six weeks following injury the patient was well with no erection difficulties. The penis looked normal, although there was a small painful lump in the base of the penis. A large urethral sound passed with no catch.

Discussion

Published reports of this injury are so few that it is difficult to draw firm conclusions as to the best treatment.

Traditional treatment is conservative, with the passage of a Foley catheter and application of a compression bandage. In cases with urethral

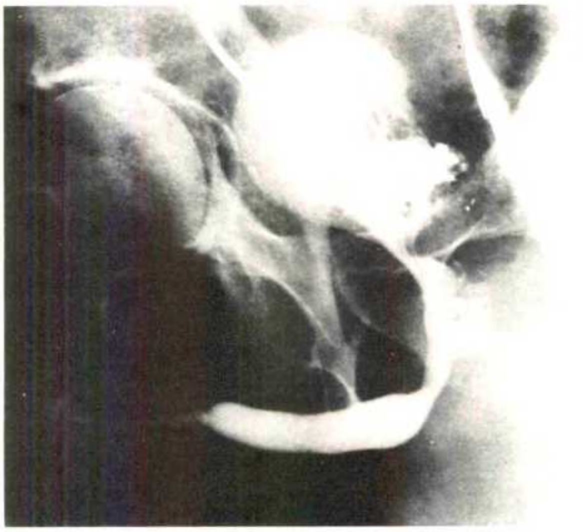

Fig. 1 Micturating cystourethrogram 3 weeks following injury (Case 1).

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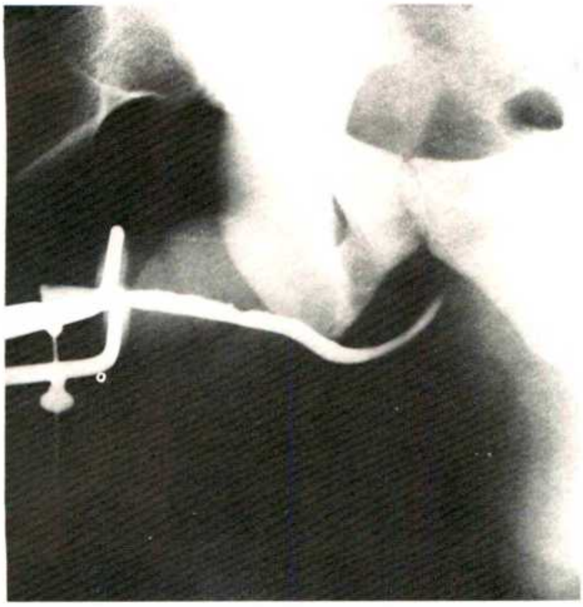

Fig. 2 Retrograde urethrogram 7 days following injury (Case 2).

injury where it is impossible to pass a Foley catheter a cystotomy is recommended. A urethral catheter can then be passed by the railroad technique (Thompson, 1954). Results from this regime are good, with only a few cases having residual deformity, but all of these cases appear to have had satisfactory intercourse subsequently (Creecy and Beazlie, 1957).

Gross *et al.* (1971) and Meares (1971) reported 3 cases of penile fracture without urethral injury treated by immediate surgical evacuation of haematoma and primary repair of the rent in the corpus cavernosum. No residual penile deformity occurred.

Gross *et al.* (1977) reported 2 cases of penile fracture with urethral laceration treated by early surgery including repair of the urethra. One case developed a stricture and neither case had any residual penile deformity.

In our 2 cases, in both of which the urethra was obviously damaged, it seemed wise to follow the teachings of the Bristol group (Mitchell, 1968). It was assumed that the urethral injury was partial and in Case 2, which was treated by the Urology Service from the outset, a urethral catheter was avoided for fear of increasing the injury. The result in Case 2 is excellent. It is contended that much of the urethral damage seen at surgery in the 2 cases reported by Gross *et al.* (1977) may have been produced by the attempted urethral catheterisation. In one of their cases the urethra was completely transected.

Review of the literature suggests that with fracture of the penis without involvement of the urethra, conservative measures lead to acceptable results. There may be a place for immediate evacuation of haematoma and repair of the corpus cavernosum but whether less deformity results must await further experience. When the urethra is damaged a urethral catheter should be avoided and the urine diverted suprapubically until the urethra is healed. Healing of the urethra can be documented by urethrography. Any advantage resulting from immediate repair of the urethra is not proven.

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Prophylactic Vasectomy

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Summary—A prospective study of the value of vasectomy with prostatectomy is presented. Vasectomy significantly reduced the incidence of epididymitis after prostatectomy in the presence of pre-operative urinary tract infection and prolonged indwelling urethral catheterisation.

Boyce and Politano (1970) recommended that "pre-operative vasectomy should be done only in the absence of infected urine and before catheterisation or instrumentation". Badenoch (1974) stated that when vas ligation was done prior to catheterisation, epididymitis did not occur. Kendall (1963) described vasectomy in patients with indwelling urethral catheters as being like "locking the barn after the horse has been stolen".

In the Sudan, the majority of patients requiring prostatectomy have urinary tract infection and an indwelling urethral catheter. Nevertheless, in the belief that vasectomy reduced the incidence of epididymitis, we carried out a prospective study on the value of vasectomy in such patients.

Patients and Methods

A series of 282 patients with benign prostatic enlargement was admitted for prostatectomy; 235 had had urinary tract infection (UTI) and an indwelling urethral catheter for at least one week before operation. Forty-seven had sterile urine and had not been catheterised.

The prostate was removed transvesically and the bladder was drained by a Foley or Gibbon urethral catheter into a clean, non-sterile infusion glass bottle. Unilateral vasectomy through a scrotal incision was carried out on all 282 patients.

Most patients were not followed up for more than 4 weeks after discharge because they came from a distance and wished to return home as soon as possible.

Results

Patients with Pre-operative UTI and Indwelling Catheter

Of the 235 patients epididymitis occurred on the ligated side in 4, on the non-ligated side in 19 and on both ligated and non-ligated side in 2 (Table 1).

Patients with Sterile Urine Pre-operatively

Of 47 patients epididymitis occurred on the ligated side in none and on the non-ligated side in 3 (Table 2).

Discussion

Organisms can reach the epididymis through the blood stream or through the sheath or lumen of

Table 1

		Ligated side	
		+	–
Non-ligated side	+	2	19
	–	4	210
where + denotes epididymitis		$P = 0.0003$	

Table 2

		Ligated side	
		+	–
Non-ligated side	+	0	3
	–	0	44

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the vas deferens and the importance of the latter route of infection has been well demonstrated. O'Conor (1935) showed silver solution in the lumen of the vas 24 h after its injection into the bladder; Hanley (1945) and Meade (1947) described urinary fistulae after vasectomy and Badenoch (1953) described what he called the vaso-epididymal reflux syndrome. Retrograde flow of urine into the vas was demonstrated by Carlton and Leader (1960) while Kreutzmann (1938) recovered bacteria from the vasa of patients with infected urine after urethral instrumentation.

Kendall (1963) demonstrated that segments of vas excised at the time of prostatectomy were sterile in the absence of urinary tract infection in patients with indwelling urethral catheters for less than 36 h, but infected in 15% of patients with urinary tract infection. Brocks *et al.* (1971) reported positive vas cultures in 54% of patients who had had urethral instrumentation but in only 13% of those who had not had urethral instrumentation. They found no evidence of infection in the vas when the urine was sterile.

Organisms already exist in the vas at the time of vasectomy in a number of patients with urinary tract infection and this proportion is significantly increased by urethral instrumentation. Some of these patients will develop epididymitis whether vasectomy is performed or not. Nevertheless, it is logical to assume that vasectomy should prevent further reflux of organisms to the epididymis.

The results of our study clearly show that in the presence of infected urine and an indwelling urethral catheter, vasectomy significantly lowers the incidence of epididymitis but does not prevent it altogether (Tables 3 and 4).

Considering the high incidence of pre-operative urinary tract infection in our patients, the incidence of epididymitis compares favourably with some of the published series (McEachern, 1958; Graham and Grayhack, 1962; Kendall, 1963).

Table 3

Ligated side		*Epididymitis*	
		Yes	*No*
Urine	Infected	6	229
	Sterile	0	47
		$P=0.59$	

Table 4

Non-ligated side		*Epididymitis*	
		Yes	*No*
Urine	Infected	21	214
	Sterile	3	44
		$P=0.78$	

Vasectomy is useful even in the presence of infected urine and indwelling urethral catheterisation, but such urological techniques as minimal instrumentation, an efficient closed drainage system, the use of small non-irritating catheters, antibiotics and adequate prostatectomy remain the first line of defence against epididymitis.

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Fournier's Gangrene

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Summary—Twenty-five cases of gangrene of the scrotum and penis have been analysed. The anterior scrotum or the whole scrotum were the areas most frequently involved. The results of seminal analyses showed marked oligozoospermia during the infective period. Haemolytic streptococcus was the most common organism. The aetiology of the disease is reviewed and "infective gangrene of the scrotum and penis" is considered to be a more suitable diagnostic label than Fournier's gangrene.

Gangrene of the scrotum has continued to be a surgical rarity since the first reports of this mystifying penoscrotal affection in 1764 (Nicholas, 1972). Fournier wrote on the subject in 1883 and described 5 cases in the following year. Randall (1920) catalogued 16 cases. Gibson (1930), Mansfield (1946), Campbell (1955), Thomas (1956), Dunaif (1964), Tan (1964), Moustafa (1967), Pryor *et al.* (1971) and more recently Buchanan (1972) have published further cases.

Idiopathic scrotal gangrene has an alarmingly sudden onset associated with severe constitutional upset, resembling cancrum oris in its aggressive and destructive nature but differing from it in that the victims of scrotal ulceration almost always enjoy good health, whereas the oral lesions affect only those in poor health. The aetiology of the idiopathic form remains elusive (Burpee and Edwards, 1972). In its secondary form there is some easily identifiable factor which precipitates an attack. Both primary and secondary types are uncommon (Moustafa, 1967; Talarico, 1970; Frier and Howie, 1972) and the hospital incidence in the South-West Province of the Cameroon is about 1:7500 out-patient consultations.

The doubtful aetiology of the condition and the limited number of studies carried out on its clinical features, complications and treatment, are all reflected in conflicting published reports. A series of 25 cases collected over a period of 10 years is presented.

Patients and Methods

All patients with scrotal pain, itching or swelling who attended out-patient clinics at the Ekona, Bota, Tiko and Buea General Hospitals in the Fako Division in the South-West Province of the Cameroon were seen. These symptoms formed the only criteria for inclusion in the study.

A history was taken which included occupation, social background and the date when the patient first felt unwell before scrotal symptoms developed. Details of past or recent trauma to the pelvis or genitalia were noted. When the diagnosis was suspected the patients were admitted for observation. In those with clinical evidence of frank disease the following details were recorded: daily approximate size of the scrotum and/or penis, dates of appearance of pitting, appearance of black patch or patches, desquamation, overt gangrene and location, dates when sloughing started, first appearance of granulation tissue and date of complete epithelialisation of lesions. A hand lens was used to detect any cracks in the skin of the scrotum and penis. The quality of penile erection was appraised. The following laboratory investigations were carried out as routine: haemogram, blood film for microfilaria or skin snip for *Onchocerca volvolus*, urine analysis and culture, plasma proteins and a semen analysis at 1, 4, 12 and 24 weeks after treatment. Antibiotic sensitivities were assessed at the onset of gangrene and thereafter if the patient was not responding well after about 10 days' treatment with a particular drug.

Results

The ages ranged from 22 to 65 years (mean 48.2).

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Name	age	Alhs	Plhs	Arhs	Prhs	AS	PS	Fundus	Whole	Shaft	Psa	Perineum	SH/SC
V.A.	22					X							
B.W.	27						X						
S.T.	30								X				
R.E.	30	X	X										
T.A.	35					X		X			X		
R.O.	35					X							
S.O.	38	X									X		
A.M.	40					X							
D.E.	40					X							
O.B.	40	X											
D.R.	42			X									
T.V.	42						X					X	
R.M.	42					X					X		
C.B.	43							X					
J.B.	45	X											
H.N.	46			X									
C.S.	47					X		X					
J.S.	48								X				
T.O.	50								X		X		
G.B.	53										X		X
W.A.	54								X				
W.M.	55								X				
T.A.	56								X	X			
S.K.	60								X				
H.N.	65										X		X

ALHS: Anterior left hemiscrotum
PLHS: Posterior left hemiscrotum
ARHS: Anterior right hemiscrotum
PRHS: Posterior right hemiscrotum
AS: Anterior scrotum
PS: Posterior scrotum
PSA: Penoscrotal angle
SH/SC: Shaft of penis & scrotum and PSA

Fig. 1 Distribution of lesions.

Lesions of the anterior scrotum and of the whole scrotum were the most frequent and the least affected area was the posterior left hemiscrotum (Fig. 1). The significance of these findings is uncertain.

Prodromal symptoms usually lasted for 1 or 2 days. Ten patients complained of low backache, 5 of a slight chill and 12 of inability to cope effectively with routine activities. In 4 cases an impending attack of malaria was suspected. Twenty patients had some symptomatic warning before the scrotal or penile symptoms and signs became manifest. In all patients the onset was dramatic and they were soon overwhelmed by the disease process. The natural history of the disease is shown in Figure 2.

Laboratory Findings

Swabs were taken at various intervals during the course of the disease (Fig. 3). Haemolytic streptococcus (16 patients) was the most frequently isolated organism; 3 patients also harboured *Staph. aureus*, one had *Esch. coli*, another had *Ps. pyocyanea* and the other a *Clostridium*. These findings are in agreement with those reported by Dunaif (1964) and Werner and Falk (1964).

Plasma Proteins. There was a fall in the albumin fraction and a rise of globulin, mostly gamma globulin, in 17 patients. Twenty-three patients had a polymorphonuclear leucocytosis; the other 2 had a lymphocytosis and examination of blood film revealed that 9 patients were positive for microfilaria. In 11 patients skin snips were positive for *Onchocerca volvolus*.

Seminal analyses (total count and estimation of sperm motility) were carried out in the majority of patients. Sixteen had counts of 20×10^6 ml or less and motility was also reduced. However, 13 of the 16 had counts above 20×10^6 ml 24 weeks later and the motility had also risen appreciably. With serious scrotal/shaft lesions the counts remained low at 24 weeks. Seven patients had initial counts of 21×10^6 ml or above and maintained these levels. One died before testicular assessment could be done.

Treatment

Antibiotic therapy was given in all cases, supplemented by conservative surgical procedures (hydrogen peroxide toilet, cetrimide or vaseline gauze followed by mercurochrome) in 12 patients, and radical surgery (undermining, debridement, split skin and/or rotation skin grafts or abdominal flaps) in the remaining 13. In the first group the results ranged from good to excellent. In the second group, where the lesions were more serious and/or extensive, the results ranged from fair to excellent.

Complications (Table)

Post-infective impotence was temporary and

Table

Types of complications	*No*	*Percentage of total*
Scrotal deformity	1	4
Penile deformity (Mild chordee)	1	4
Urethral fistula	1	4
Skin depigmentation	1	4
Post-Infective impotence	2	8
Psychoses:		
During disease process	22	88
After cure	6	24
Painful erection	1	4
Toxaemia	1	4

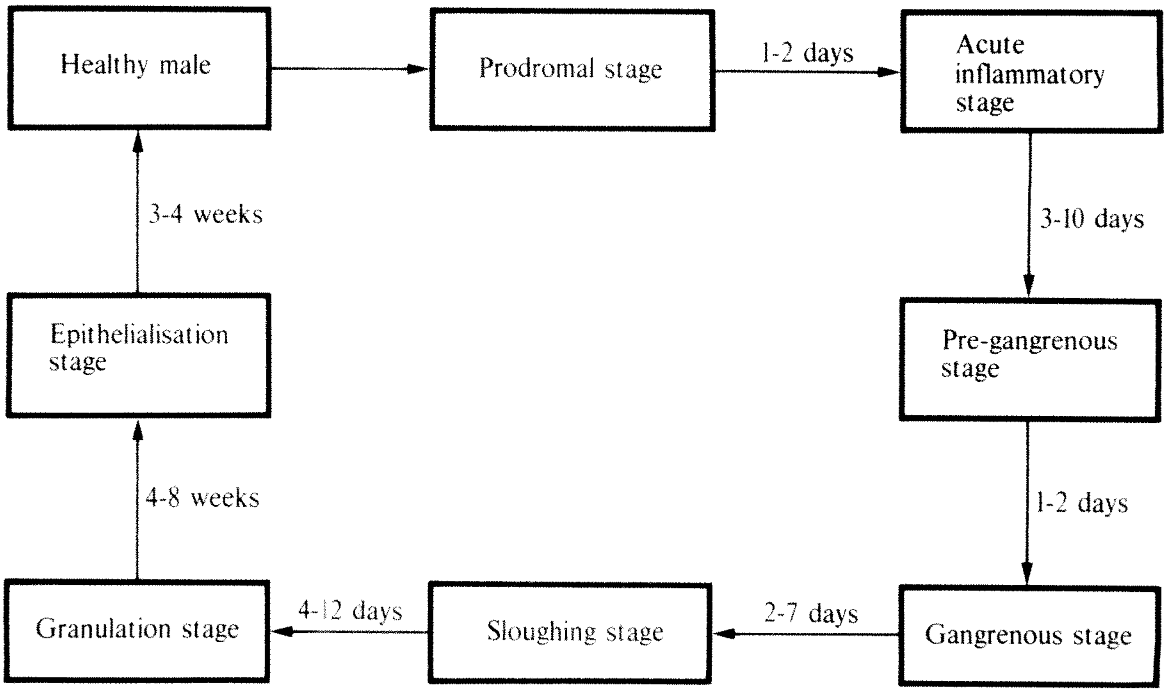

Fig. 2 Diagrammatic representation of the natural history of Fournier's gangrene.

recovery usually occurred by the twelfth week. Painful erection was also transient and disappeared with simple advice and reassurance. The patient with scrotal deformity took his own discharge from hospital when the acute stage of the disease was over, only to return because of the deformity. The minimal penile bend was due to cicatrisation and required no treatment. Skin depigmentation was embarrassing and psychologically disturbing to the patient.

The commonest complication in the series was psychological. During the active stage of the disease the symptoms were mainly depressive, but were replaced by anxiety neuroses as the patient improved or was cured.

Discussion

Until antibiotics were used in the management of Fournier's gangrene the mortality was between 20 and 30% (Randall, 1920). Only one patient in the present series died and this fatality might have been avoided if all the treatment prescribed had been available.

The behaviour of seminal fluid in patients with Fournier's gangrene has not been studied before. The impairment of spermatogenesis is probably due to several factors such as toxaemia, exposure of the testes to a warmer environment and peri-testicular sepsis.

The aetiology of Fournier's gangrene has been mostly speculative and still remains obscure. Pryor *et al.* (1971) maintain that most cases are secondary to some infectious process but admit that only in a third of these has a means of entry been found. It has been found as a secondary infection in several diseases such as measles and small pox (Werner and Falk, 1964) and erysipelas, sepsis of the navel, balanitis and chickenpox (McCrea, 1945). Thomas (1956) has stated that it may be secondary to minor surgical procedures in the penoscrotal area or secondary to chancroid, retrocaecal appendicitis and acute haemorrhagic pancreatitis. Frier and Howie (1972) considered it an opportunist disease in a case of myeloma. It is tempting to speculate, as did Marshall *et al.* (1953), that the high cold haemagglutinins found in a patient with myeloma might have precipitated thrombosis and subsequently gangrene. Dunaif (1964) thought that an obliterative endarteritis was responsible, but this was probably the result rather than the cause of an infective process. Burpee and Edwards (1972) stated that urogenital infection, ischiorectal abscess and fistula may be

Names	*Esch. coli*	*Ps. pyocyanea*	Haemolytic *Streptococcus*	*Staph. aureus*	*C. diphtheriae*	Non-haemolytic *Streptococcus*	*Proteus*	*Clostridium*	*Str. faecalis*
J.B.			X	X					
S.T.	X		X						
D.R.							X		X
O.B.			X						
T.A.			X						
R.O.		X		X					
D.E.			X					X	
T.A.				X	X				
G.P.			X						
V.A.			X						
B.W.			X						
S.K.						X			
T.V.			X	X					
W.A.	X								
R.E.				X			X		
H.N.			X						
A.M.		X	X						
T.O.				X			X		
J.S.			X					X	
H.N.				X		X	X		
R.M.			X						
W.M.			X						
S.O.			X						
C.S.			X	X					
C.B.				X			X		

Fig. 3 Distribution of infecting organisms.

causative factors. Randall (1920) considered the infection to be the result of synergistic activity of a microaerophilic, non-haemolytic streptococcus, but the problem is not so much the infecting organisms as the route by which they reach the tissues. Are they intrascrotal commensals which burst into sudden pathogenic activity with altered host resistance, or are they residents of the loose folds of scrotal skin where they pose a potentially lethal complication with the tiniest epidermal puncture? Buchanan (1972), Tan (1964) and Talarico (1970) have considered that lack of hygiene and low socio-economic conditions are prime factors in the causation of the disease and this view is supported by the findings in the present series. However, these factors alone do not necessarily produce infection—they merely provide a fertile field. For infection to flourish, bacteria must be present in sufficient strength to overwhelm host defence mechanisms.

Two patients with filariasis had excessive scrotal pruritus and nail scratch marks on the scrotum. In 3 other patients who were filaria-positive the scrotum was found to be unhealthy and they had previously suffered from mild penoscrotal elephantiasis. Four patients had microscopic abrasions seen by the aid of a hand lens and 2 patients had 2 to 3 epilated hair follicles. In all, 11 patients had some visible scrotal anomaly.

Nicholas (1972), in his monograph on the subject, emphasises the ability of organisms to enter a portal too minute for clinical detection. Idiopathic gangrene and secondary gangrene of the scrotum may harbour the same organisms; in one there is an obvious macroscopic portal, whereas in the other it is of microscopic dimensions.

It therefore seems unnecessary to adhere too rigidly to the concept of primary (or idiopathic) and secondary types of the disease and Fournier's use of the word "idiopathic" is not strictly correct if, as seems likely, all cases result from transfer of organisms through the epidermis. The term "infective gangrene of the penis and scrotum" is suggested as a more acceptable title.

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Faecal and Introital Bacteria and Urinary Tract Infection

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Summary—The faecal, introital, and urinary bacterial flora have been studied in 3 normal women and 5 women with recurrent urinary infection. In the normal women urinary abnormalities were uncommon, but the patients regularly had episodes of bacteriuria and pyuria, only a quarter of which were symptomatic. Symptoms tended to be associated with high white cell excretion rates and with the longer episodes.

Introital colonisation was heavier and more frequent in the patients than in the control subjects. Organisms recovered from the urine had previously colonised the introitus in most cases.

It appears that symptomatic episodes constitute only a small part of the disease process in patients with recurrent urinary tract infection.

Urinary tract infection in women is a distressingly common condition. Most of the infections are ascending (Hinman, 1966) and the organisms originate in the patient's own bowel. It has been suggested that one of the factors that predisposes to the development of infection is colonisation of the vaginal vestibule with urinary pathogens (Stamey *et al.*, 1971; Stamey, 1973), though other workers have been unable to demonstrate a close relationship between introital enterobacteria and urinary infection (O'Grady *et al.*, 1970; Marsh *et al.*, 1972). This study was undertaken in an attempt to elucidate the relationship between the faecal flora, introital colonisation and the development of urinary tract infection.

Patients and Methods

Five women, aged 21 to 43 years, were studied; each had suffered at least 2 attacks of bacterial cystitis in the 3 months before the start of the investigation. All had normal excretion urograms and in all the residual urine was less than 2 ml (Barnard *et al.*, 1973). The 3 controls, aged between 21 and 39 years, had no history of urinary tract infection.

All of the individuals taking part in the investigation gave twice-weekly stool samples, twice-daily introital swabs and daily early morning urine samples. The investigation lasted on average 89 days for each patient (range 67 to 107 days).

Specimens of faeces were inoculated onto MacConkey agar and examined for coliform organisms, enterococci and micrococci. Five colonies of each colonial type of coliform were identified by their biochemical reactions (Cooke *et al.*, 1969) and examined for haemolysin production (Cooke, 1968). Selected strains of *E. coli*, having biochemical and haemolytic characteristics similar to strains subsequently found in the urine, were serotyped using 150 0 antisera and 50 H antisera (Bettelheim and Taylor, 1969). Catalase-negative Gram-positive cocci which were isolated on MacConkey agar were considered to be enterococci. Micrococci were identified by their biochemical reactions (Baird-Parker, 1966).

Swabs were taken from the vaginal introitus morning and evening using swabs moistened in nutrient broth. These were wiped around the external meatus, with the labia held apart, and were immediately placed in Stuart's transport medium. They were inoculated onto MacConkey and blood agar and the organisms were examined in the same way as those from the faeces. Where several colonial types of *E. coli* were isolated, serotyping was carried out only on those with biochemical and haemolytic reactions similar to the organisms subsequently recovered from the urine. The number of organisms recovered from

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the introital swab was expressed semi-quantitatively (O'Grady *et al.*, 1970).

Clean catch early morning urine specimens were obtained daily and refrigerated until examined. Cells were counted without centrifugation. The urine was inoculated onto MacConkey agar using a standard loop. The organisms isolated were examined in the same way as those from faeces except that only one colony of each colonial type was examined.

Results

Urinary Tract Infection

The urine was considered to be abnormal if more than 10 pus cells/mm^3 were present or if there was a significant bacteriuria ($>10^5$/ml). Episodes of pyuria or bacteriuria were relatively common in the patients, occurring on average once every 10 days. There was little difference between the patients in the frequency of episodes, the range being from an average of one episode in 7 days to one in 12 days. Of the 44 episodes occurring during 446 patient days, 38 were pyuric and 30 bacteriuric. In only 13 episodes did patients suffer from symptoms of infection. These symptomatic episodes were distributed between the 5 patients as follows: 5, 3, 2, 2, 1. The 30 episodes of bacteriuria were associated with the following organisms: *E. coli* 16, *Strep. faecalis* 8 and micrococci 6.

In the controls there were 2 episodes of pyuria occurring in 2 individuals. There were no episodes of bacteriuria and no symptoms of infection (Table 1).

In the patients, symptoms tended to be associated with a high white cell excretion rate and with longer episodes of pyuria or bacteriuria (Table 2). Seven of the bacteriuric episodes consisted of only one infected specimen and none of these was associated with symptoms.

Table 1 The Incidence of Pyuria, Bacteriuria and Symptoms of Urinary Tract Infection in Patients and Controls

	No. of persons	*No. of patient days*	*No. of episodes of pyuria*	*No. of episodes of bacteriuria*	*No. of episodes associated with symptoms of UTI*
Controls	3	191	2	0	0
Patients with UTI	5	446	38	30	13

Table 2 The Association Between the Duration of Bacteriuria, the Duration and Severity of Pyuria and the Development of Symptoms of Urinary Tract Infection

	No. of episodes associated with symptoms of UTI	*No. of episodes not associated with symptoms of UTI*
Pyuria of 1-3 days	5	23
Pyuria of 4 days or more	8	2
Bacteriuria of 1-3 days	4	21
Bacteriuria of 4 days or more	5	0
Pyuria of 10-60 cells/mm^3	5	19
Pyuria of more than 60 cells/mm^3	8	6

Introital Colonisation

The colonisation of the introitus with *E. coli* was heavier and more frequent in the patients than in the controls. *E. coli* was recovered from 16% of introital swabs from patients and from 6% of swabs from the controls. A heavy growth was obtained from 7% of the patients' swabs and 1% of the swabs from the controls.

Urinary and Introital Bacteria

The results of the examination of introital swabs in the days preceding a bacteriuric episode were available in 28 of 30 episodes. Organisms considered to be similar when identified biochemically were present in the introitus and the urine in 23 of these 28 episodes. On 16 occasions *E. coli* was found in the introitus before appearing in the urine. On 12 occasions *E. coli* from both sources were serotyped and in only one case was the serotype different. The period of introital colonisation preceding a bacteriuric episode was variable. Eight of the episodes of bacteriuria followed a period of introital colonisation exceeding 5 days' duration.

Urinary and Faecal Bacteria

For 28 bacteriuric episodes faecal specimens were obtained during the 6 days preceding the episode and for 11 of the episodes 2 specimens were obtained during this time. Similar organisms, when identified as described, were found in 19 of the 28 episodes. The urinary organism was *E. coli* in 16 of the episodes; serotyping was carried out in 11 of these and the similarity of the organisms was confirmed in 5. Micrococci were isolated from the urine on 6 occasions; they were never isolated from the faeces.

Haemolysin Production

Eight per cent of isolates of *E. coli* from the faeces were haemolytic. There was no difference between the controls and the patients in the faecal carriage rate of haemolytic *E. coli*. Eighteen per cent of isolates from the introitus were haemolytic. This comprised 21% of the 1166 isolates from patients and 2% of the 150 isolates from the controls. No *E. coli* were isolated from the urine of the controls. Thirty-four per cent of the *E. coli* isolates from the urine of the patients were haemolytic.

Discussion

The initial aim of the investigation was to study in detail the relationship between introital colonisation and the development of urinary infection, but the finding which emerged most clearly was the frequency of asymptomatic infection in patients who were also suffering from recurrent symptomatic disease.

Asymptomatic bacteriuria in non-pregnant women has been studied and it has been shown (Asscher *et al.*, 1972) that symptomatic infection develops more frequently among bacteriuric than control subjects. In this investigation we have shown that in women with recurrent symptomatic infection the symptomatic episodes constitute less than a third of the episodes of bacteriuria and pyuria. Although symptoms were most frequently associated with bacteriuria and pyuria of more than 3 days' duration and with pyuria of more than 60 cells/mm^3, the possibility arises that these very frequent attacks of infection, which are untreated because they are asymptomatic, may be of importance in the development of the disease. Radiological disease appears to be more common in wholly asymptomatic patients (O'Grady *et al.*, 1972). From the small number of patients studied here it appears that the distinction between asymptomatic and symptomatic patients may not be a clear one, as symptomatic patients also have many asymptomatic episodes.

The relationship between introital colonisation and the development of urinary tract infection has been studied by a number of workers (O'Grady *et al.*, 1970; Stamey *et al.*, 1971; Marsh *et al.*, 1972; Stamey, 1973) and some evidence has been obtained that introital colonisation may be of importance in the development of urinary tract infection. The results presented here support this view as introital colonisation was more frequent and heavier in the women with recurrent urinary infection that in the controls. In addition, the previous isolation of the infecting organism from the introitus was regularly demonstrated, as was the development of infection following a period of introital colonisation of more than 5 days' duration.

Although it is generally accepted that the bowel is the source of many of the organisms causing urinary infection, we were unable to demonstrate in the faeces the serotype of *E. coli* which subsequently caused infection in 6 of the 11 patients in whom this was attempted. The reasons for this are not clear. Many of the investigations demonstrating faecal carriage of the infecting strain have been carried out subsequent to the development of the infection (Grüneberg *et al.*, 1968; Bettelheim *et al.*, 1971) and few prospective studies have been done. It has been shown that under certain conditions the faecal coliform population may change rapidly (Cooke *et al.*, 1969) and although specimens of faeces were obtained twice-weekly it may be that the infecting strain was present in the faeces for such a short time before the development of the infection that it was not detected.

The results for haemolysin production are similar to those obtained previously (Cooke and Ewins, 1975). The introital isolates from the patients were commonly haemolytic (21%) whereas those from the controls were not (2%). Thirty-four per cent of the urinary infecting strains were haemolytic. It has been shown (Cooke and Ewins, 1975) that introital strains that subsequently cause infection are more frequently haemolytic than those which do not and the present findings support this view.

This study of a small number of patients provides evidence that women with bacteriuria cannot be divided clearly into symptomatic and asymptomatic groups, as patients with symptoms also undergo asymptomatic episodes of bacteriuria and pyuria which outnumber the symptomatic episodes.

Acknowledgements

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British Journal of Urology (1979), **51**, 321

Case Reports

Leiomyosarcoma of the Bladder

Non-epithelial tumours of the bladder of mesenchymal origin are very rare, comprising 1% or less of all bladder tumours (Jewett, 1970). Among them over 50% are sarcomas of one type or another.

Case Report

A 63-year-old male presented with a recent history of gross, total, painless haematuria. Physical examination was negative, apart from revealing a rather feeble man. Laboratory findings confirmed the severe blood loss. An excretory urogram showed normal renal outlines. The cystogram demonstrated irregularity of the dome of the bladder, due to a large filling defect. Cystoscopy revealed a solid tumour, 5 cm in diameter, situated at the dome of the bladder.

Suprapubic exploration of the bladder was carried out and the tumour was excised by partial cystectomy. Post-operatively the patient presented no problems and he was discharged 20 days after the operation. Histopathological examination of the excised specimen showed a leiomyosarcoma of the urinary bladder (Fig.) consisting mainly of spindle-shaped cells arranged in interlacing fascicles.

Eight months after the operation cystoscopic examination showed no recurrence of the disease.

Comment

Primary sarcomas of the urinary bladder are rather uncommon, highly malignant lesions. Leiomyosarcoma occurs in patients at any age, but is more common during the fifth and sixth decades. Males are affected twice as often as females (Brown, 1965).

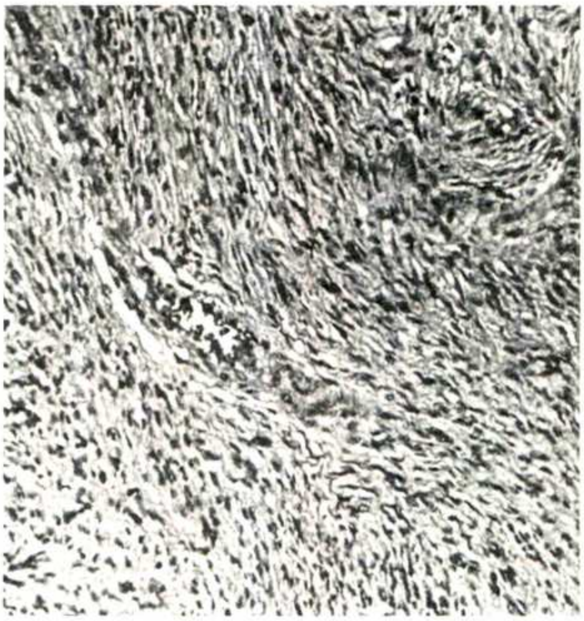

Fig. (×125.)

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British Journal of Urology (1979), **51**, 322-323

Giant Hydronephrosis

As a result of improved medical care, most cases of hydronephrosis are now diagnosed before the kidney is large enough to produce a visible swelling. Occasionally, however, massive distension of the kidney is encountered which warrants the term "giant hydronephrosis". The present report relates to such a case in an adult male where the hydronephrosis contained 42½ litres of urine.

Case Report

M.K.B., a 34-year-old male school teacher, attended the clinic because of abdominal distension. He had no other complaints and carried out his work without much hindrance. He had been born with a large abdomen and since childhood it had been increasing in size. Previously, a diagnosis had been made of ascites due to liver disease, but no investigations or treatment had been carried out.

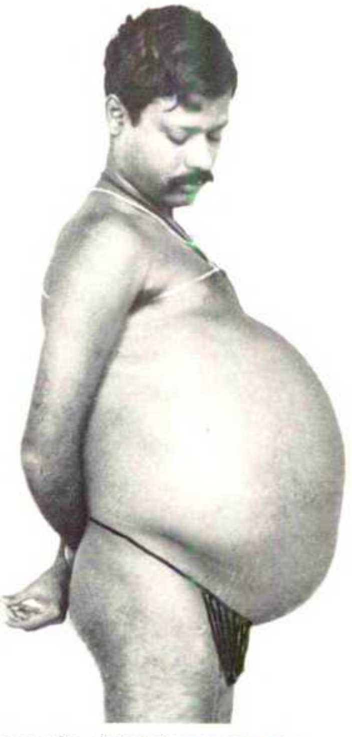

Fig. Appearance of patient before treatment.

On examination, the abdomen was hugely and tensely distended (Fig.) The left margin of a massive swelling could be palpated. The swelling itself was dull to percussion; there was a narrow resonant strip in the left flank. A fluid thrill could be elicited but there was no shifting dullness. The patient's height was 171 cm, weight 98 kg, chest circumference 97.75 cm and abdominal circumference 151 cm (right half 77.5 cm and left half 73.5 cm). The distance from the xiphisternum to the pubis was 62.25 cm and from the xiphisternum to the umbilicus 41.25 cm. The blood pressure was 190/120 mmHg.

Laboratory investigations showed the haemoglobin to be 14 g%, white cell count normal, ESR 3 mm in 1 h, blood sugar 96 mg% and blood urea 27 mg%. Liver function tests were normal. The urine contained a trace of albumin and occasional pus cells. X-ray of chest demonstrated a wide thorax, with vertical compression. Intravenous urography showed no concentration by the right kidney; the left kidney was normal, with an incomplete duplication of the ureter. A follow-through barium meal revealed that the alimentary tract was displaced to the left side of the abdomen. The investigations confirmed the clinical diagnosis of a giant hydronephrosis of the right kidney.

Treatment

It was considered that nephrectomy was required but that sudden decompression of the abdomen might be hazardous because of its possible effects on cardiorespiratory function. A two-stage procedure was therefore pursued. Under local anaesthesia a polythene tube was inserted through a cannula into the hydronephrosis and the swelling was decompressed slowly over a period of 2 days, after which time the tube became blocked and was removed. Thirty-five litres of clear, straw-coloured urine were drained; it contained a trace of albumin and occasional pus cells and was sterile on culture. In spite of the gradual lessening of the abdominal distension the patient's condition gave cause for anxiety. A few hours after the beginning of kidney drainage, palpitations and dyspnoea developed and the blood pressure fell. On the second day, gastric dilatation occurred. After 5 days of supportive therapy the patient's condition stabilised and a chest X-ray showed an improved appearance.

Nephrectomy was performed under general anaesthesia 2 weeks after the decompression of the hydronephrosis. The kidney was exposed extraperitoneally through a long, transverse abdominal incision. The hydronephrotic sac was very thin and was inadvertently opened. Seven and a half litres of residual urine were aspirated. Palpation of the interior of the sac revealed that it extended below to the pelvis and the left iliac fossa; above, the right lobe of the liver was compressed and displaced to the left. With some difficulty, the sac was dissected free. It was found that the right ureter, like the left, was bifid and there was an obstruction at the site of its bifurcation. The kidney tissue was almost completely destroyed, there being only a thin, pancake-like area of parenchyma over the upper aspect of the sac. Following nephrectomy, the wound was closed with drainage. Blood transfusion was given during and after the operation. Apart from a brief period of post-operative shock, the patient made an uneventful recovery and the wound healed by first intention. He was subsequently taught abdominal exercises to regain muscle tone. At the time of discharge from hospital, 4 weeks after operation, the patient weighed 64 kg and the abdominal circumference was 97 cm. The urine was sterile. The blood pressure was 150/95 mmHg. When last seen, 1½ years after nephrectomy, the patient was well, his blood pressure was 140/90 mmHg and his appearance was normal.

Comment

A giant hydronephrosis may fill the entire abdomen, as in our patient, and differentiation of the condition from ascites may then be difficult on clinical examination alone. In a review of the literature, Tombari *et al.* (1968) noted that a correct pre-operative diagnosis had been made in only 46% of cases. In the case reported by Kaushik and Sachdeva (1973) the hydronephrosis contained 8 litres of urine; in our patient it contained 42½ litres. Sorrentino (1966) made a plea for conservative surgical management of giant hydronephrosis, especially in young patients and in bilateral cases. However, in the present case the left kidney was normal and it was not considered that the thin disc of parenchyma on the right was worth preserving. We believe that a most important aspect of the management of giant hydronephrosis is the two-staged approach described. A one-stage nephrectomy, by causing a sudden fall in intra-abdominal pressure, could cause severe cardiorespiratory distress and alimentary tract dysfunction. Even slow decompression of the kidney produced these effects to some degree in our patient. The post-operative problems following the nephrectomy on the other hand were much less.

Summary

A case of congenital, unilateral giant hydronephrosis containing 42½ litres of urine in an adult male is reported.

Diagnosis and management are discussed.

Because of the possible effects of sudden abdominal decompression, a plea is made for a two-stage procedure. The hydronephrosis is first decompressed slowly by drainage and nephrectomy is then performed after the patient's cardiorespiratory and alimentary systems have been stabilised.

Acknowledgements

We are grateful to the Secretary of our Institution and to our colleagues in the X-ray department who coped with the technical problems of radiological investigations in a large, heavy patient.

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British Journal of Urology (1979), **51**, 324

A Giant Prostatic Tumour

In the female the fibroid uterus and the cystic ovary may attain enormous dimensions, while in the male prostatic enlargement is a common occurrence although seldom of such dramatic proportions. However, there have been reports of benign prostatic enlargement up to 820 g by Ockerblad (1946) and of prostatic carcinoma up to 1755 g by Krawitt (1973).

The present case concerns a tumour which gave rise to considerable diagnostic perplexity.

Case Report

An African man of about 66 years of age complained of an abdominal swelling which he had first noticed 2 years previous to his admission. At laparotomy a tumour mass weighing 1888 g arising from the prostate gland was removed (Fig. 1). The patient made a good recovery and is alive and well at the time of writing this report, 10 months after the operation. Subsequent histology of representative blocks of the tumour revealed a leiomyoma (Fig. 2).

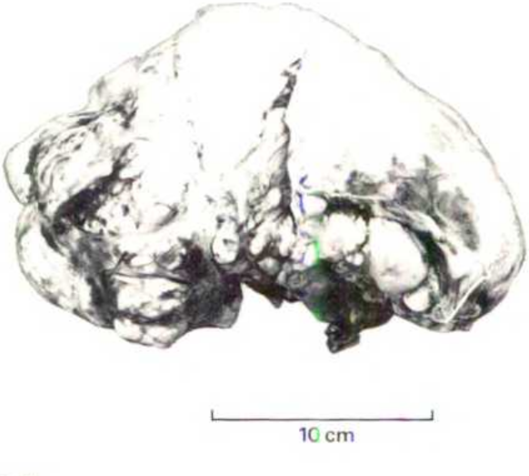

Fig. 1

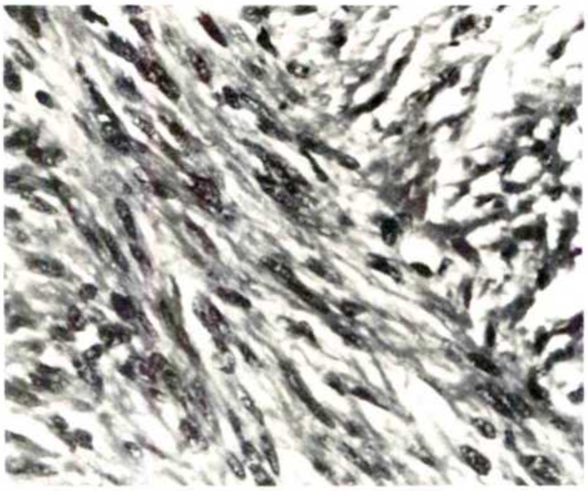

Fig. 2

Comment

This is believed to be the largest prostatic tumour reported to date.

Acknowledgements

I wish to thank Dr Sebina, Permanent Secretary of the Ministry of Health, Botswana, for his kind permission to publish this case. I wish to thank also Dr A. M. Merriweather and Lt.-Col. J. B. Stewart, RAMC, for their comments and assistance.

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British Journal of Urology (1979), **51**, 325

Leukoplakia in a Diverticulum of the Urinary Bladder

Case Report

A 45-year-old male presented with complaints of cloudiness of urine, a sense of retention, and rice-sized whitish-grey foreign bodies in his urine. Excretory urogram and cystoscopy revealed a diverticulum behind the right ureteric orifice (Fig. 1). The diagnosis of leukoplakia in the diverticulum was established pre-operatively following cytological examination of the foreign bodies in the urine and of washings obtained directly from the diverticulum (Fig. 2). Diverticulectomy including the bladder wall was carried out. In order to prevent recurrence, a total of 150 mg Bleomycin was administered over 10 weeks. This resulted in mild side effects, including slight skin thickening on the legs and slight depilation on the scalp.

Comment

The mucosa in the diverticulum of the urinary bladder may be irritated by urinary stasis, chronic inflammation and stone (Campbell and Harrison, 1970).

When compared with leukoplakia of the pelvis, ureter, bladder and urethra, leukoplakia in this segment has a higher incidence of carcinoma. Early diagnosis is therefore essential in adult cases. Cytological staining of the tissues collected directly from the diverticulum using endoscopy could provide an exact diagnosis. Complete diverticulectomy and administration of Bleomycin brought about satisfactory results. The patient is alive and well 6 years later and the bladder appeared normal at recent cystoscopy.

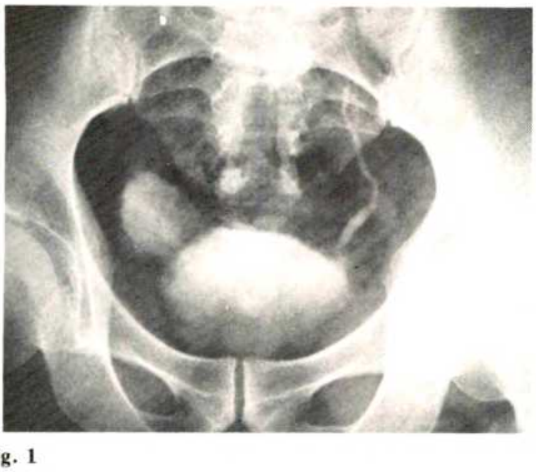

Fig. 1

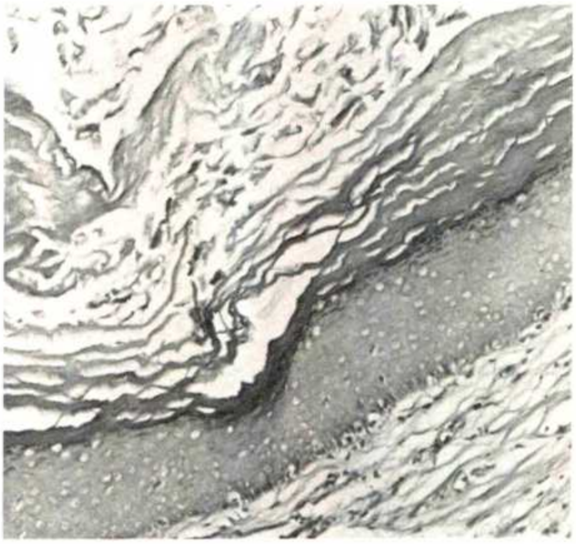

Fig. 2 (H and E × 100.)

Reference

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British Journal of Urology (1979), **51**, 326

Leiomyosarcoma of Ureter Presenting as Acute Renal Failure

Case Report

A 50-year-old male was admitted with right loin pain and anuria of 8 days' duration. On examination there was tenderness in the right lumbar region. No masses were palpable. The blood urea was 50 mmol/l. Plain X-ray of the abdomen showed an enlarged right kidney; the left kidney was not seen. Retrograde ureteric catheterisation was attempted but was unsuccessful. The patient was treated with haemodialysis for 8 h and, with a diagnosis of acute obstruction to a single kidney, the right ureter was explored. There was a multilobulated, firm mass overlying the upper third of the ureter. The ureter was dissected free. It was found to have a narrow segment, which was excised, and an end-to-end anastomosis was done. Histological examination of the segment of ureter showed a leiomyosarcoma (Fig.).

The patient regained normal renal function postoperatively. An intravenous pyelogram showed hydronephrosis of the right kidney and a non-functioning left kidney. The patient has since been lost to follow-up.

Comment

Leiomyosarcoma of the ureter is a rare tumour and only 10 cases have been reported in the literature (Shah and Kothari, 1971). Eight patients have been post-menopausal women. The common symptoms are flank pain and the presence of a lump. Acute renal failure as the presenting feature has not been recorded before.

The tumour may grow around the ureter in a concentric manner and the ureteric lumen may remain patent until a late stage (Werner *et al.*, 1959). The tumour is very malignant and extensive secondary metastases have been noted at autopsy (Alznauer, 1955). The treatment of choice is radical dissection and nephroureterectomy. This could not be done in our patient because the growth involved his only functioning kidney.

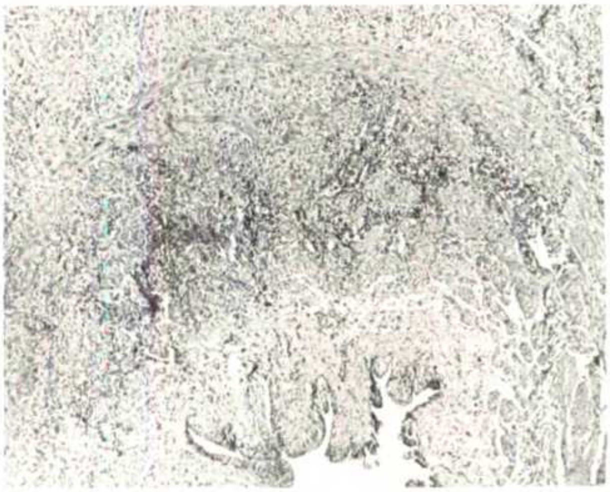

Fig. Tumour arising from wall of ureter. (H and E × 120.)

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British Journal of Urology (1979), **51**, 327

Inverted Papilloma in a 14-Year-Old Male

Case Report

A 14-year-old male presented with painless, gross, total haematuria. Five years earlier he had had a right nephroureterectomy because of the destructive effects of infection and reflux. Cystoscopy revealed a polypoid, fleshy, pink tumour hanging from the dome of the bladder, just to the right of the midline. The tumour was resected transurethrally and its base fulgurated. Repeat cystoscopies over 2 years have revealed no evidence of tumour recurrence.

The specimen removed weighed 4.8 g. Microscopically, the surface of the tumour was covered by a slightly hyperplastic but smooth epithelial surface. The bulk of the tumour was composed of broad sheets of stratified epithelial cells and anastomosing cords of varying thickness. The component cells were generally regular in size and mitosis was not a notable feature. The outer layer of cells in the tumour cords was cuboidal, with a palisading effect in some areas. There was a relatively scant, intervening, fibrovascular stroma, and a slight degree of inflammatory infiltrate was present. Microcysts were present in the tumour and some contained a homogeneous eosinophilic material. The cysts were lined by flattened cuboidal cells (Figs. 1 and 2).

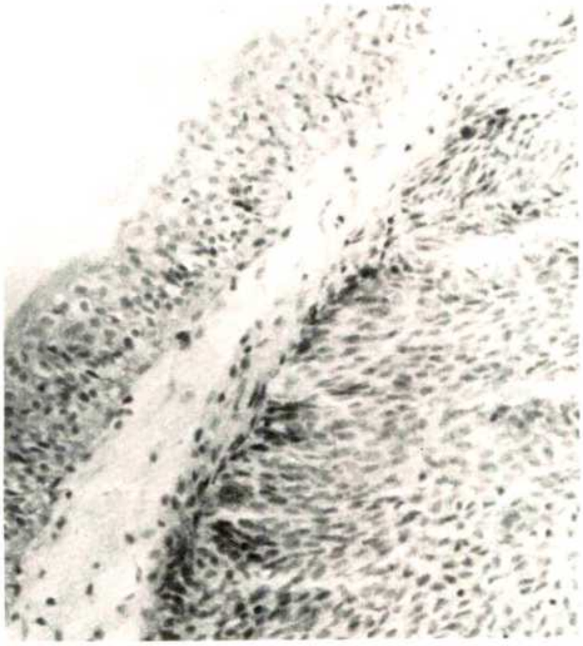

Fig. 1 Hyperplastic surface epithelium with underlying tumour in a scant fibrovascular stroma. (H and E × 100.)

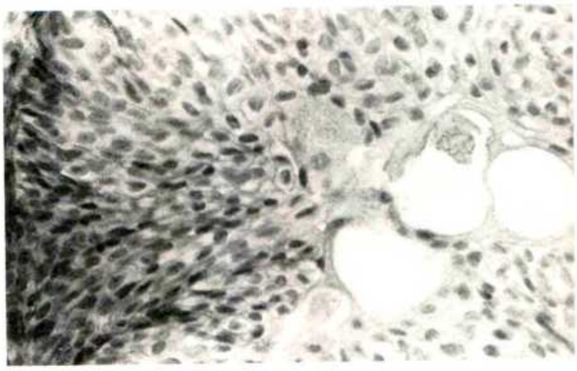

Fig. 2 Component cells are regular; microcysts are present. (H and E × 250.)

Comment

Inverted papilloma was described first by Potts and Hirst in 1963, and by several authors since then. The largest series was reported by Cameron and Lupton in 1976. The present case is unique because of its occurrence in a 14-year-old male and because of its location on the dome of the bladder.

References

Cameron, K. M. and Lupton, C. H. (1976). Inverted papilloma of the lower urinary tract. *British Journal of Urology*, **48**, 567-577.

Potts, I. F. and Hirst, E. (1963). Inverted papilloma of the bladder. *Journal of Urology*, **90**, 175-179.

The Author

R. R. Francis, Division of Urology, Royal Alexandra Hospital, Edmonton, Alberta, Canada.

British Journal of Urology (1979), **51**, 328

Conferences and Courses

First International Congress on Hormones and Cancer

Rome, Italy. 4-6 October 1979.

Further information from: Professor S. Iacobelli, Laboratorio di Endocrinologia Molecolare, Instituto di Clinica Obstetricia e Ginecologica, Universita Cattolica, Via Pineta Sacchetti 644, I-00168 Roma.

Congress of the Hungarian Society of Urology and Nephrology

Budapest, Hungary. 10-13 October 1979.

Further information from: Dr I. Soltesz, Department of Urology, University of Debrecen, H-4012 Debrecen.

International Symposium

Vienna, Austria. 23 and 24 November 1979.

The following topics will be discussed: latest treatment of urethral stricture in the male; indications, technique, post-operative care and late results with staghorn calculi.

Further particulars from: Dr P. Porpaczy, c/o Vienna Medical Academy, Alser Strasse 4, A-1090 Vienna, Austria.

Combined Meeting of BAUS and the Canadian Urological Association

Montreal, Canada. 21-25 June 1981.

In order to make provisional plans about transport and a short pre-congress tour, it is essential to have some idea of the number of British members likely to attend this meeting.

Any members of BAUS who are interested in attending should communicate with Mr J. L. Williams, Honorary Secretary, BAUS, Royal College of Surgeons, Lincoln's Inn Fields, London WC2, as soon as possible.

Meeting of the International Society for Dynamics of the Upper Urinary Tract

Antwerp, Belgium. 2-3 October 1979.

Further particulars from: Dr B. Coolsaet, Noordheuvel 50, 2170 Gooreind, Belgium.

American Urological Association: Meeting of the Northeastern Section

Montreal, Canada. 23-26 September 1979.

Further particulars from: Dr Kenneth J. MacKinnon, Royal Victoria Hospital, 687 Pine Avenue, W., Montreal, Quebec, Canada H3A 1A1.

Annual Meeting of the Swiss Society for Urology

Biel, Switzerland. 8-10 November 1979.

Further information from: Prof. Dr K. Bandhauer, Urologische Klinik Kantonsspital, CH-9007 St Gallen.

International Symposium. Current Treatment of Urethral Stricture in Man

Vienna, Austria. 23-24 November 1979.

Further information from: Dr P. Porpaczy, c/o Wiener Medizinische Akademie, Alser Strasse 4, A-1090 Wien.

31st Meeting of the German Society for Urology

Munich, Germany. 17-20 October 1979.

Further information from: Dr Hartung, Urologische Klink und Poliklinik, Ismaninger Strasse 22, 8000 Munich 80, Germany.

British Journal of Urology (1979), **51**, 329

Mr J. D. Fergusson

With the death on 20 April of Mr J. D. Fergusson—Jerrie Fergusson to his innumerable friends—this country lost one of its outstanding senior urologists.

For over 30 years Jerrie Fergusson was an essential part of the British urological scene which he enhanced both personally and professionally in an exceptional number of ways. He was an excellent practical urologist; he was the first Director of Teaching and Research at the Institute of Urology of the University of London from 1951 to 1971; he contributed extensively to the urological literature; and he had special talents as an editor of urological textbooks.

In 1948 he was appointed Assistant Editor of this Journal and in 1967 he succeeded David Band as Editor; under his guidance the Journal continued to flourish with rapid expansion of its sales particularly in the United States. At the end of his 5 years in office he was appointed Honorary Consulting Editor. He was Honorary Editorial Secretary to the British Association of Urological Surgeons no less than 3 times—1952 to 1955, 1961 to 1964, and 1967 to 1969.

Although he was highly critical in his assessment of papers submitted for publication, he was always kind, helpful and encouraging to the unsuccessful author; it was said that his rejection letters were almost a pleasure to receive.

From 1957 to 1960 he was Honorary Secretary and during the last 3 years of his editorship, from 1969 to 1972, he was Vice-President and then President of the Association.

In 1977 he was awarded the St Peter's medal for outstanding services to urology.

The present editorial team are very much aware of the standards set by Jerrie Fergusson; our efforts to maintain these are our best tribute to his memory.

W. Keith Yeates

Book Reviews

Clinical Hypertension. N. M. Kaplan. Second edition. Pp. ix + 405. Baltimore: Williams and Wilkins Co., 1978. Price £26.65; US $41.00.

The second edition of this excellent review of "Clinical Hypertension" is clinically orientated and focuses on all of the significant advances that have been made during the past 10 years. As is fitting, over half of the book is devoted to essential hypertension and the pathophysiology, clinical management and treatment are discussed in detail. The less common, but nevertheless important secondary causes of hypertension, namely renal disease, renovascular conditions, primary aldosteronism, pheochromocytoma, coarctation and Cushing's disease, and the effect of pregnancy and the pill on hypertension are discussed. Finally, there is a chapter on hypertension in childhood and adolescence.

The figures and illustrations are excellent and there is a comprehensive and up-to-date index following each chapter. This book is highly recommended to practitioners requiring a day-to-day knowledge of the management of hypertension and to those specialists who wish to study various aspects of hypertension in depth.

Drugs and Renal Disease. Monographs in Clinical Pharmacology. S. M. Bennett, G. A. Porter, S. P. Bagby and W. J. McDonald. Pp. 185. Edinburgh: Churchill Livingstone, 1978. Price £12.00.

The main topics covered in this short monograph are modification of drug dosage in renal failure, drug-induced renal disease and the drug therapy of renal disease. Drugs are often used incorrectly in patients with renal disease in whom the incidence of adverse drug reactions is increased. The chapter on modification of drug dosage in renal failure should therefore be of particular value. For most important groups of drugs there are detailed tabulations of plasma half-lives and recommended dosage reductions in patients with mild, moderate and severe renal failure. Errors are inevitable, but occasionally recommendations are potentially dangerous as, for example, the advice to reduce the dose of methotrexate by only 50% in patients with a creatinine clearance of less than 10 ml/min. Insufficient attention is given to the consequences of cumulation of drug metabolites, and the authors seem unaware of the extent of this problem.

The chapter on nephrotoxicity is disappointing with little emphasis on mechanisms, predisposing factors and prevention. Analgesic nephropathy is dismissed in little more than one page and it is incorrectly stated that phenacetin is a major metabolite of paracetamol (acetaminophen). This book appears to have been written for the non-specialist reader and, as such, it fills an important gap. References are provided at the end of each chapter. These are appropriate, not excessive in number and most are reasonably up to date.

The HLA System. *British Medical Bulletin* (Volume 34, Number 3, September 1978, pp. 213-324). London: British Council. Price £5.00.

The aim of this volume is to provide a general view of the HLA system, but with particular emphasis on the clinical applications. There are 17 contributions from recognised British authorities in the field, each being a concise, up-to-date mini-review.

The format and style of this volume follow that of its distinguished predecessors; the terse, succinct style of the presentation will make it hard going for the non-expert and, regrettably, the majority of clinicians. To some extent, therefore, the stated aim of emphasising the clinical applications must be frustrated. In this context the balance leans very heavily towards disease associations (37 pages), with transplantation (12 pages) taking very much second place; bone marrow transplantation and its problems receive only a passing mention. It is also disappointing that none of the distinguished contributors address themselves specifically to the question we are continually asked (and ask ourselves)—what is the clinical value of a particular disease association? This is a significant omission from a volume which lays emphasis on clinical applications.

However, these comments should not detract from the uniformly excellent contents, which include a number of very helpful summary tables. This volume is highly recommended to all workers in the field and reference copies should be made available in all departmental libraries.

Books Received

Multiple Sclerosis. The Facts. W. Bryan Matthews. Pp. 103. Oxford: Oxford University Press. 1978. £3.50.

Incontinence. A Burden for Families with Handicapped Children. J. Bradshaw. Pp. 46. London: Disabled Living Foundation. 1978. £1.50.

Conversion Table—S.I. units

Old units			*Conversion factor multiply by:*		*S.I. units*	
Constituent	*Normal range*	*Units*	*Old to new*	*New to old*	*Normal range*	*Units*
Venous blood						
Albumin	3.5-5.5	g/100 ml	10	0.1	35-55	g/l
Bicarbonate (total)	24-30	mEq/l	1	1	24-30	mmol/l
Bilirubin	0.1-0.8	mg/100 ml	17	0.059	2-14	μmol/l
Calcium	8.6-10.5	mg/100 ml	0.25	4	2.15-2.65	mmol/l
Chloride	100-107	mEq/l	1	1	100-107	mmol/l
Cholesterol	140-240	mg/100 ml	0.026	38.5	4.0-6.5	mmol/l
Creatinine	0.6-1.4	mg/100 ml	88	0.0114	55-125	μmol/l
Glucose	65-95	mg/100 ml	0.056	18	3.5-5.5	mmol/l
Iron	110-130	μg/100 ml	0.18	5.6	circa 20	μmol/l
Magnesium	1.4-1.8	mEq/l	0.5	2	0.70-0.90	mmol/l
Phosphate	2.5-4.5	mg/100 ml	0.32	3.1	0.8-1.4	mmol/l
Potassium	3.8-5.2	mEq/l	1	1	3.8-5.2	mmol/l
Protein (total)	6.5-8.0	g/100 ml	10	0.1	65-80	g/l
P.B.I.	3.75-7.5	μg/100 ml	79	0.0127	300-600	nmol/l
IgG	500-1600	mg/100 ml	0.01	100	5.0-16.0	g/l
IgA	125-425	mg/100 ml	0.01	100	1.25-4.25	g/l
IgM	50-180	mg/100 ml	0.01	100	0.5-1.8	g/l
Sodium	136-149	mEq/l	1	1	136-149	mmol/l
Transferrin	150-300	mg/100 ml	0.01	100	1.5-3.0	g/l
Triglyceride	60-140	mg/100 ml	0.0113	88.5	M2.0 P<1.5	mmol/l
Uric acid	2-7	mg/100 ml	0.06	16.7	0.1-0.4	mmol/l
Urea	15-40	mg/100 ml	0.17	6.0	2.5-6.5	mmol/l
Arterial blood						
Base excess	−3-+3	mEq/l	1	1	−3-+3	mmol/l
PCO_2	32-46	mmHg	0.135	7.5	4.5-6.0	kPa
PO_2	80-100	mmHg	0.133	7.5	10.5-13.5	kPa
Urine outputs/24 h						
Calcium	200	mg	0.025	40	5	mmol
Creatinine	1-2	g	8.8	0.113	9-18	mmol
5HIAA	3-17	mg	5.23	0.19	16-90	μmol
Inorganic P.	1000	mg	0.032	31	30	mmol
Magnesium	100	mg	0.041	24	4.2	mmol
Potassium	70	mEq	1	1	70	mmol
Protein	<0.05	g	1	1	<0.05	g
Sodium	200	mEq	1	1	200	mmol
Urea	25	g	17	0.06	400	mmol
Uric acid	500	mg	0.006	167	3.0	mmol
VMA	<7	mg	5.05	0.2	<35	μmol

Kidney Transplantation

Principles and Practice

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May 1979, xviii+310pp., £17.50

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This book presents the current position of renal transplantation from the point of view of the practising physician, transplant surgeon, nephrologist, tissue typer, virologist or bacteriologist. The book is comprehensive in the sense that a person entering a transplant unit for the first time could get an overall grasp of kidney transplantation, ranging from the surgical techniques to the diagnosis and pathology of rejection. Thus the book should be of value to all who are involved in the various aspects of kidney transplant programmes, be they doctors, scientists or nurses.

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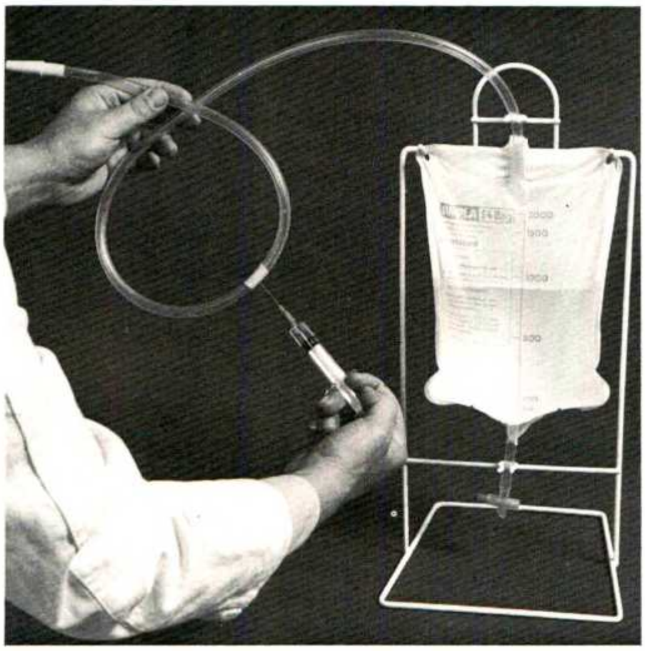

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INFECTIONS OF THE URINARY TRACT

Edward H Kass & William Brumfitt, editors

International in scope, the 45 papers in this volume are drawn from the Third International Symposium on Pyelonephritis, held in London in 1976.

Infections of the Urinary Tract represents the most complete collection of current research available on the subject, comprising studies of the pathogenesis, microbiology, immunology, and life history of such diseases as bacteriuria, prostatitis and pyelonephritis. The efficacy of screening programs are also discussed as well as various treatment strategies, including the effects of such drugs as tobramycin and trimethoprimsulfamethoxazole. *Edward H Kass is Professor in the Department of Medicine, Harvard University; William Brumfitt is Professor in the Department of Medical Microbiology, Royal Free Hospital, University of London.*

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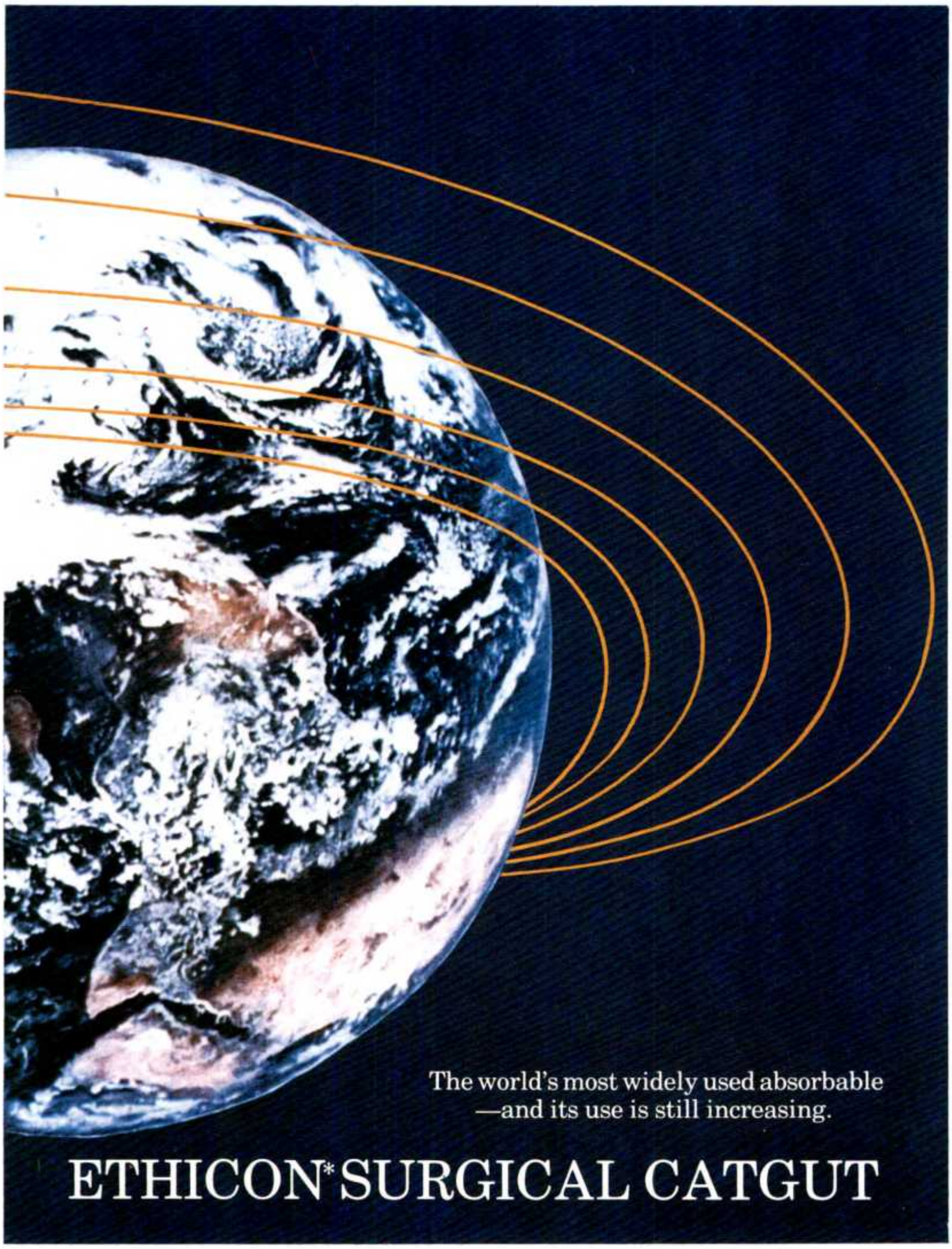
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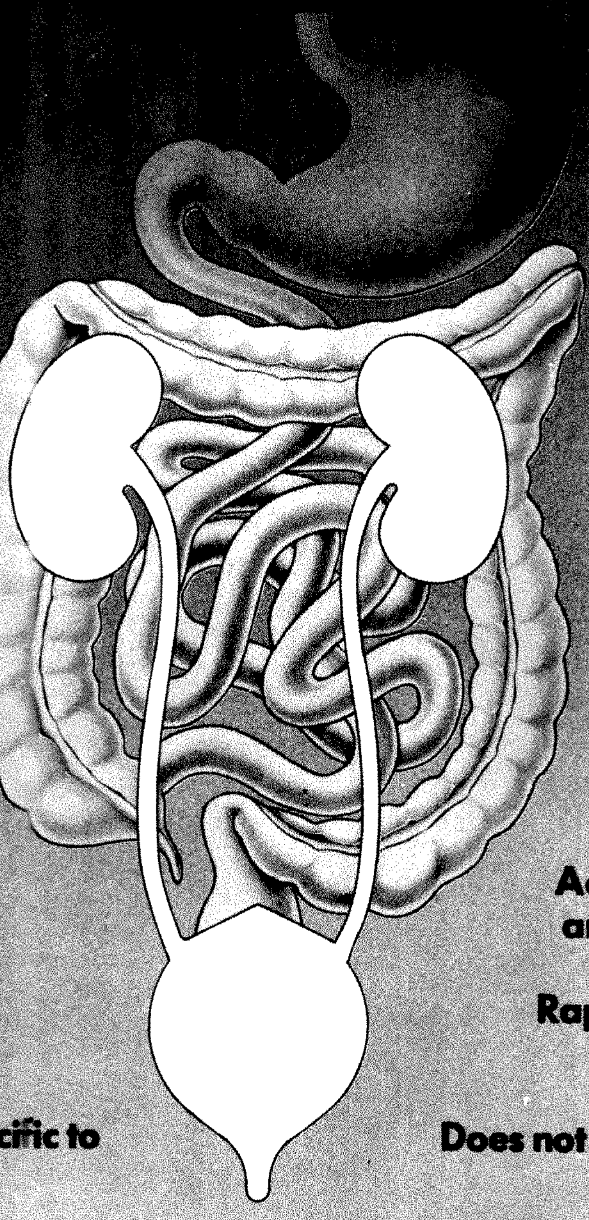

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Dosage Therapeutic. Adults 20ml 4 times daily.
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Bodyweight		Average age for weight	Dose to be taken 4 times a day
lb	kg		
10-30	5-13	3-30 months	2.5ml
30-50	13-23	2½-6 years	5ml
50-80	23-36	6-11 years	10ml
80-110	36-50	11-14 years	15ml

Prophylactic. One quarter to one half of therapeutic dose.
Contra-indications Infants under one month should not be given nitrofurantoin. Contra-indicated in patients suffering from severe renal impairment.
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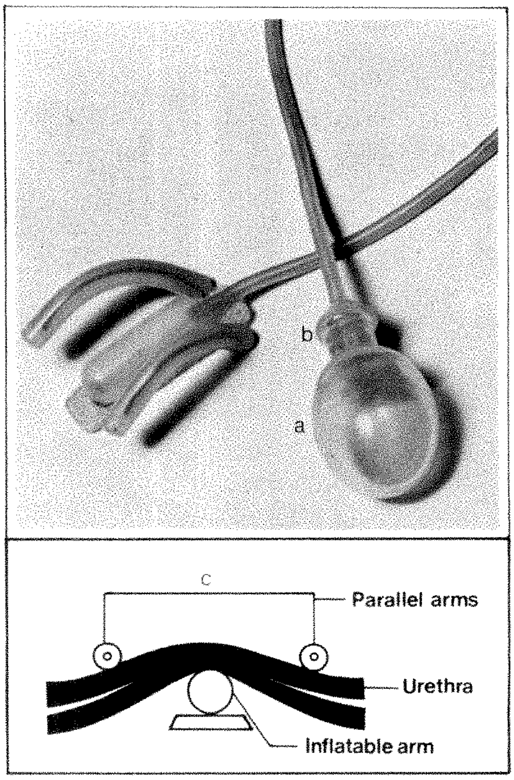

a) reservoir bulb and valve are situated in the scrotum squeeze to occlude urethra

b) squeeze to release urethra

c) parallel arms and inflatable arm fit over and under urethra

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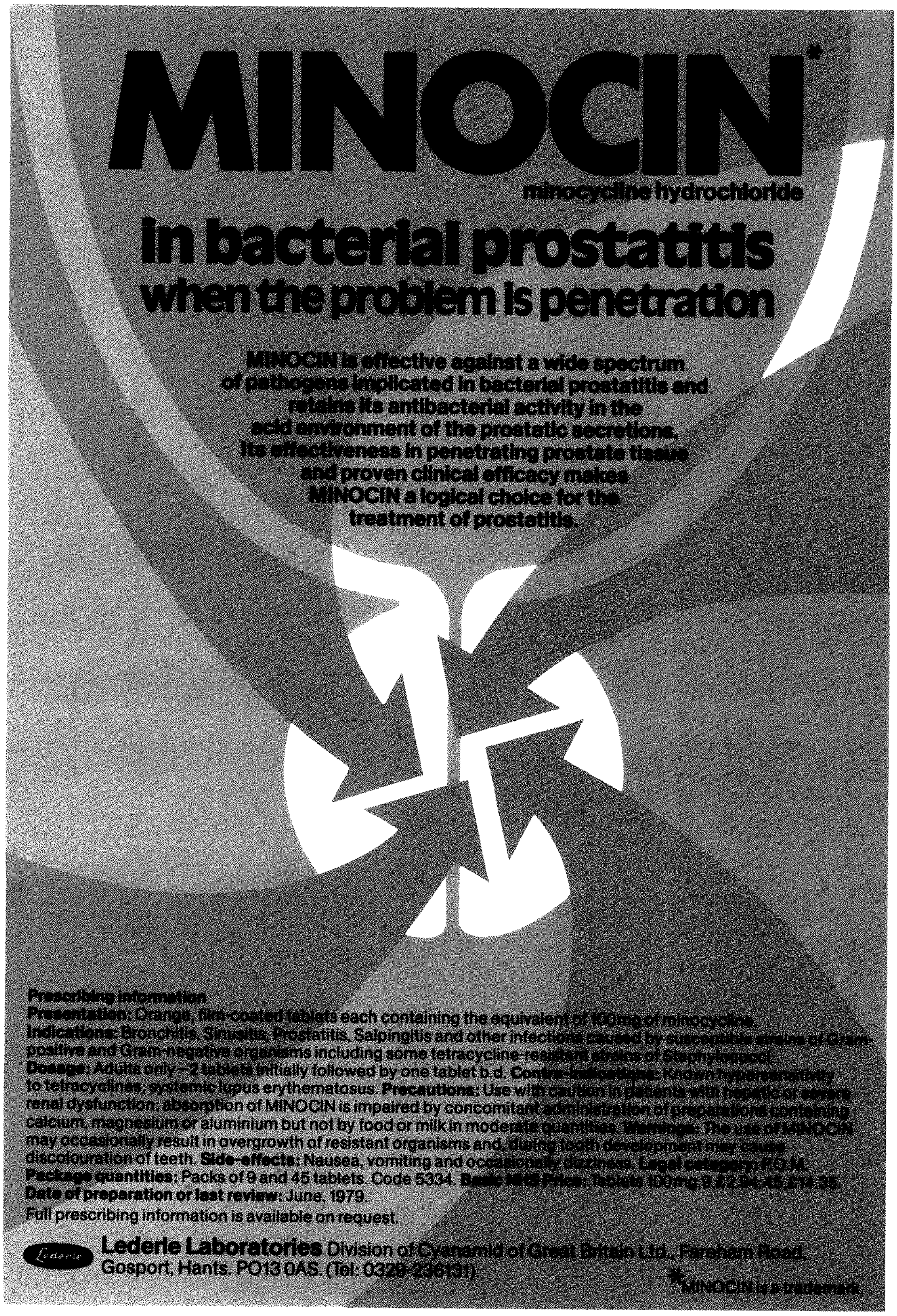

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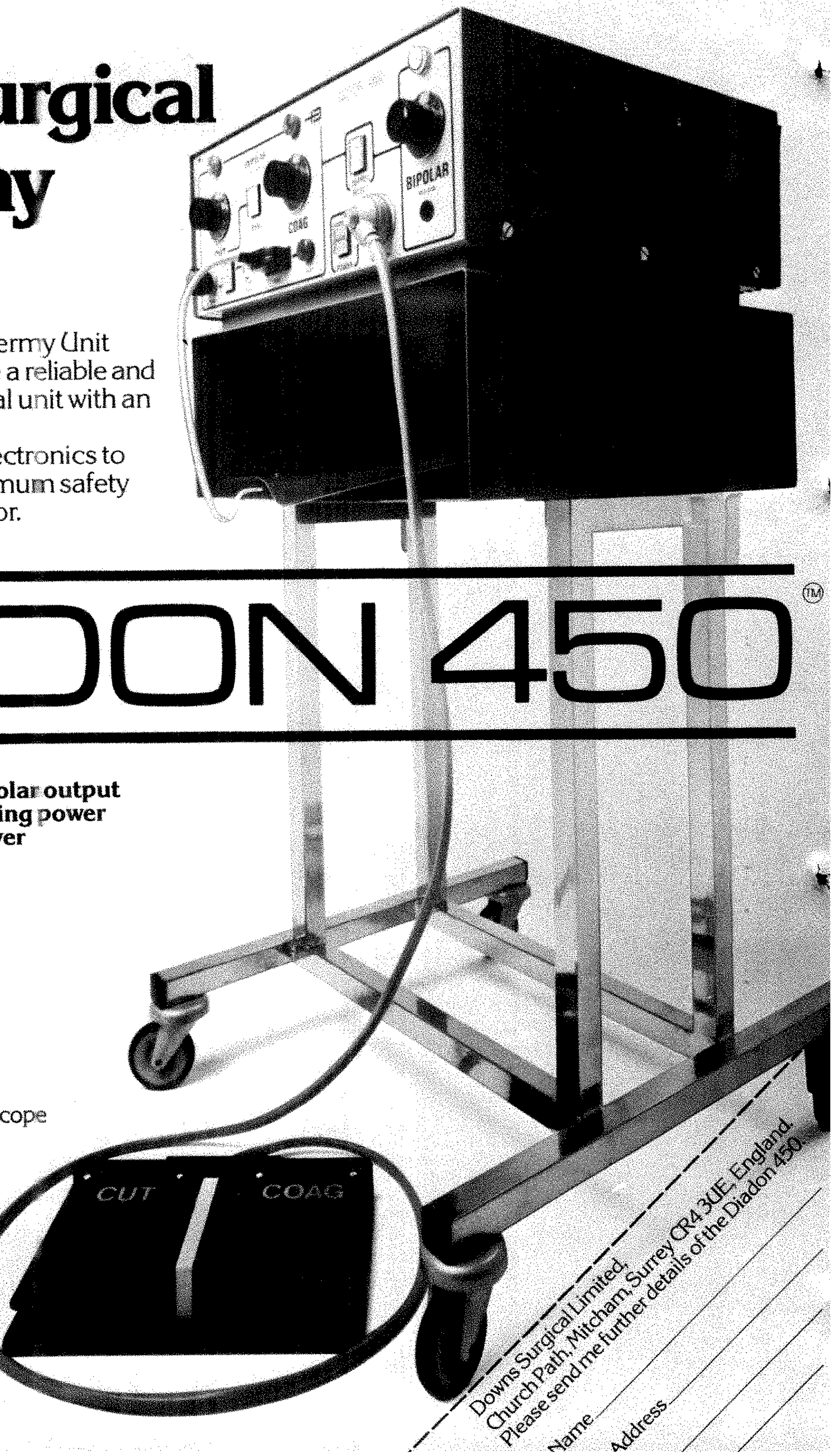

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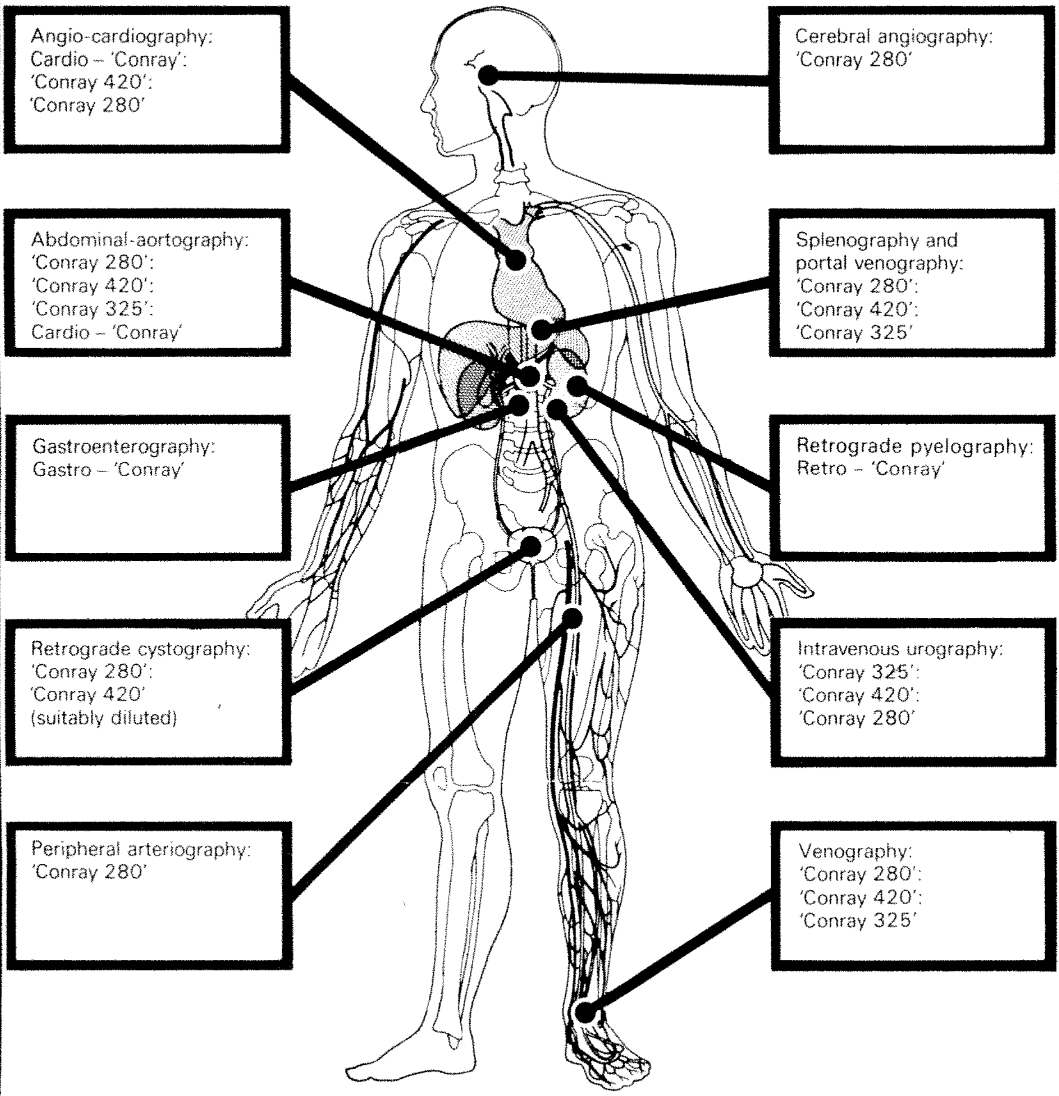

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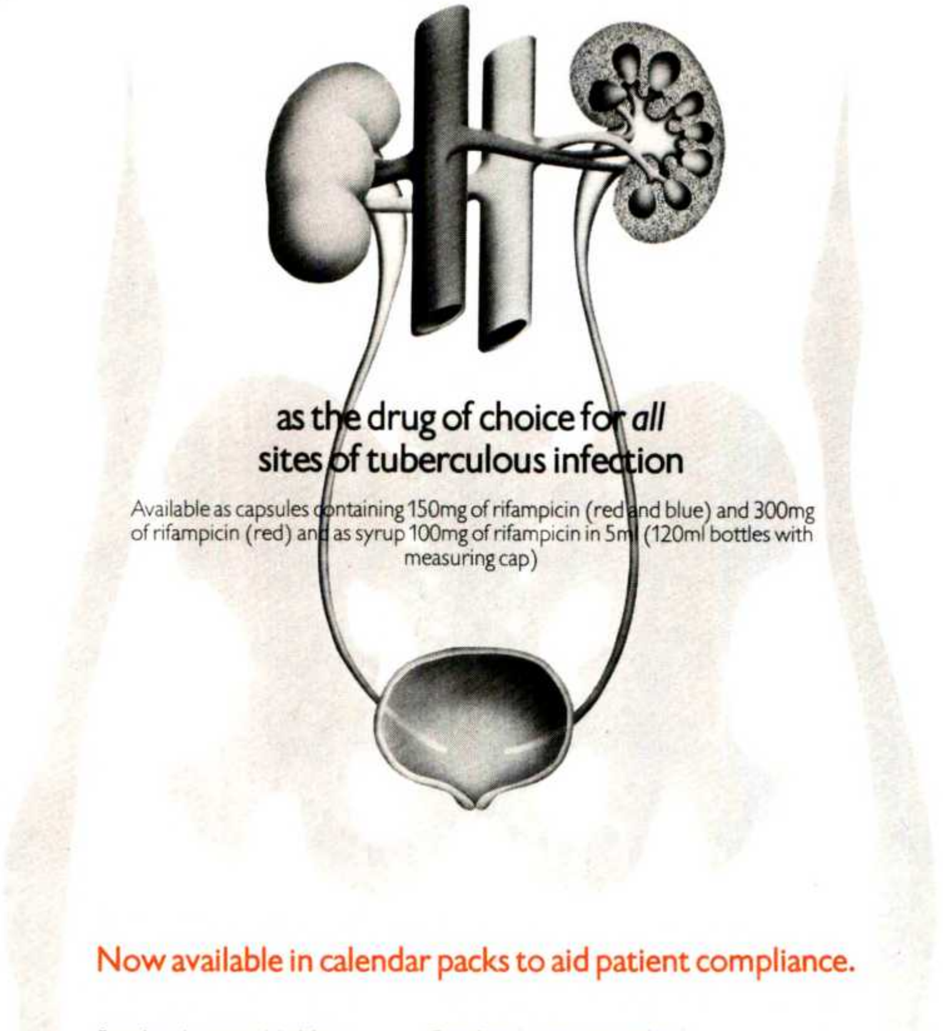

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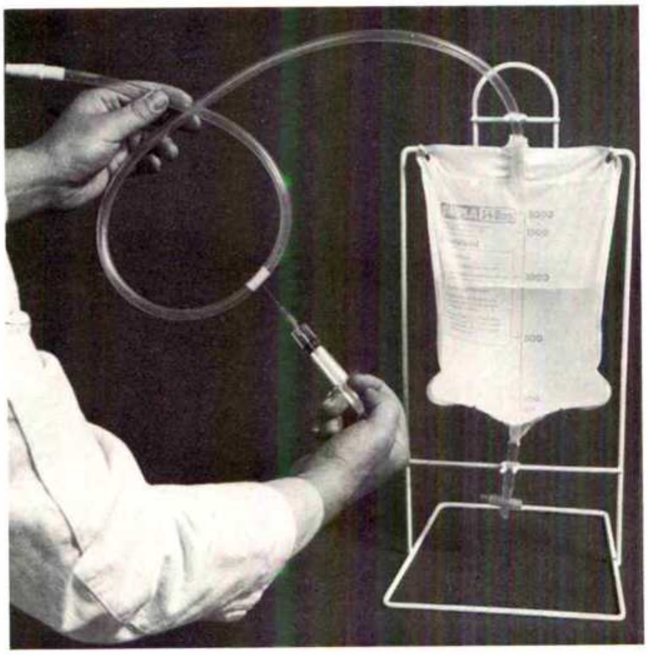

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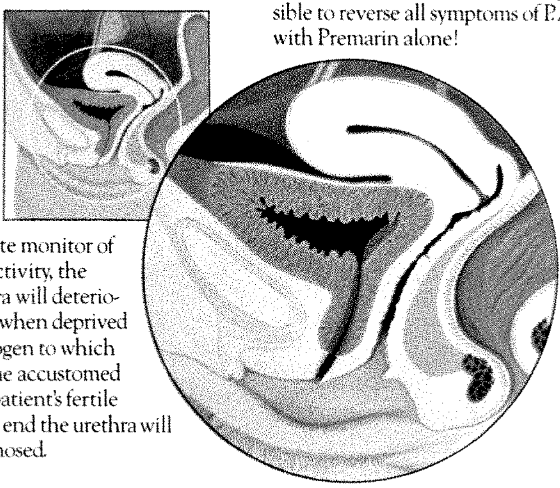
Untreated, these atrophic changes can be devastating and demoralising in their effect.[2]



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References:
1. Willington, F. L. The Practitioner. 220, 739, 1978.
2. Smith, P. J. B., Ayerst Medical Library Vol. 2, No 2, 1978.
3. Smith, P. J. B., The Practitioner. 218, 97, 1977.

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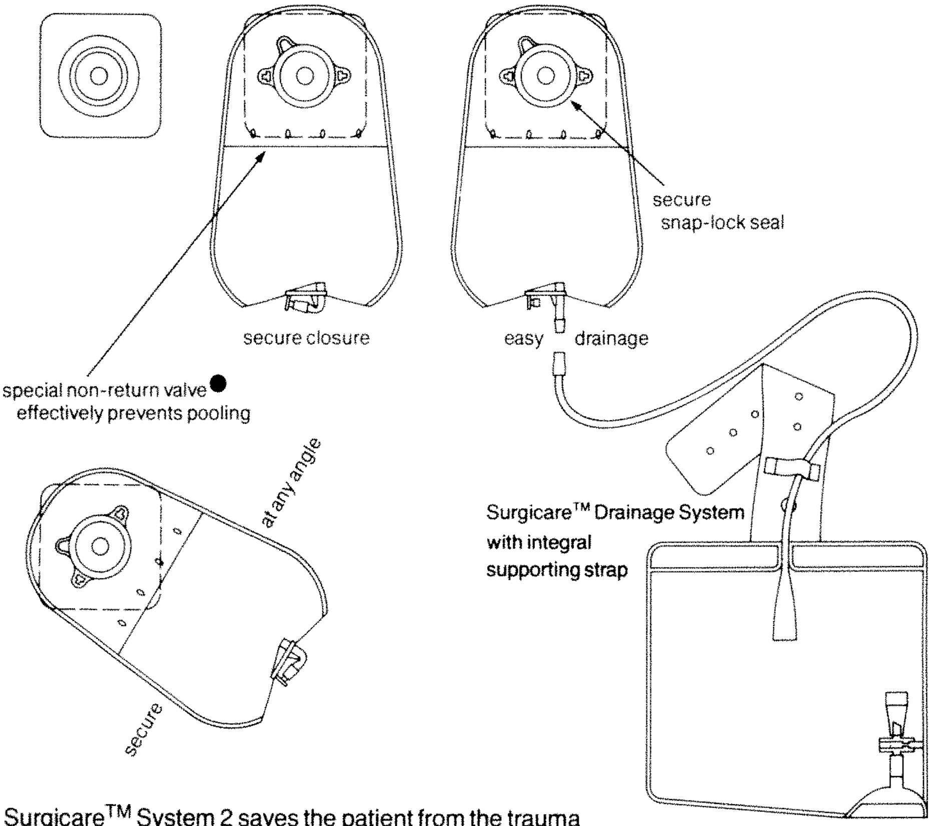

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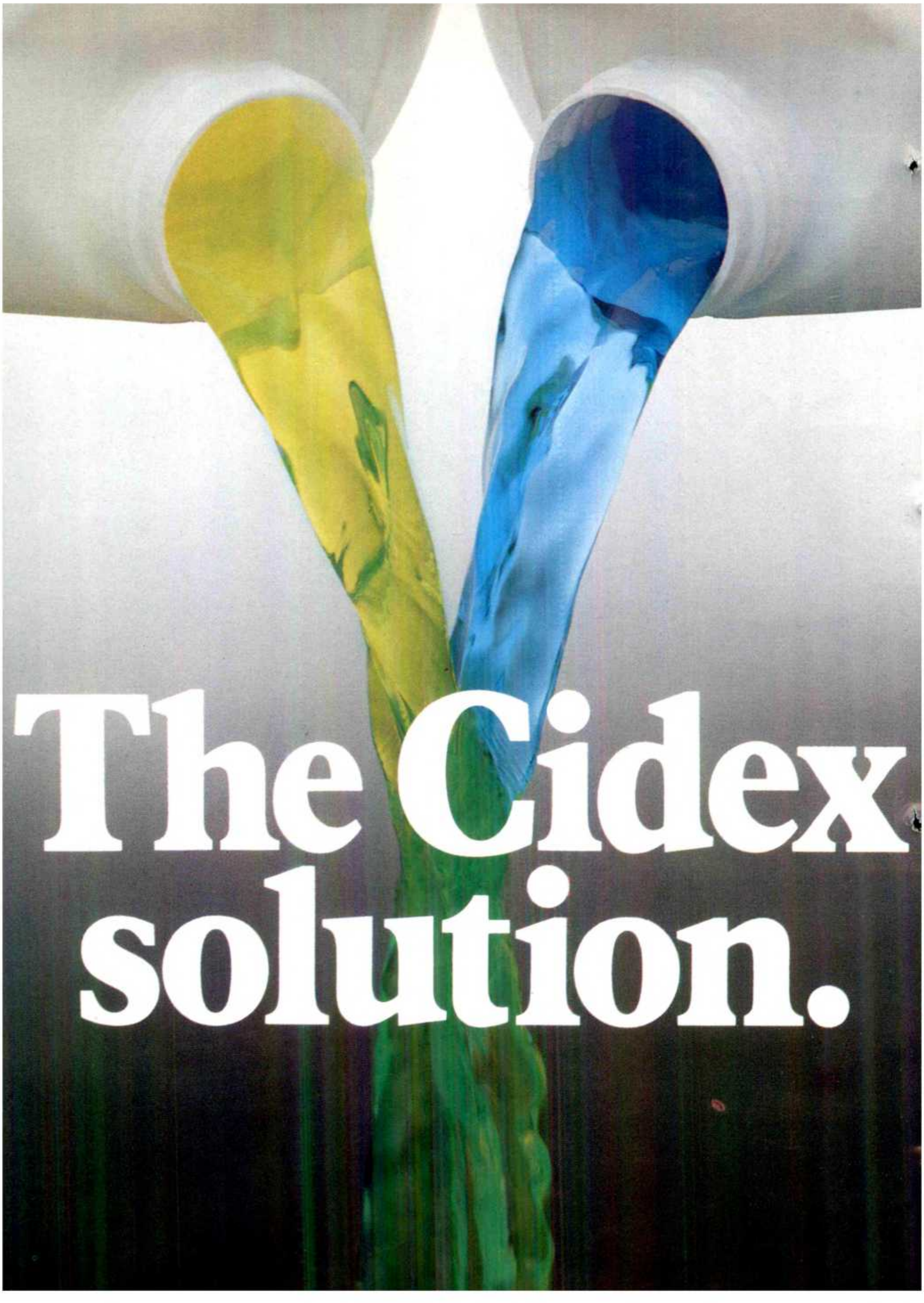
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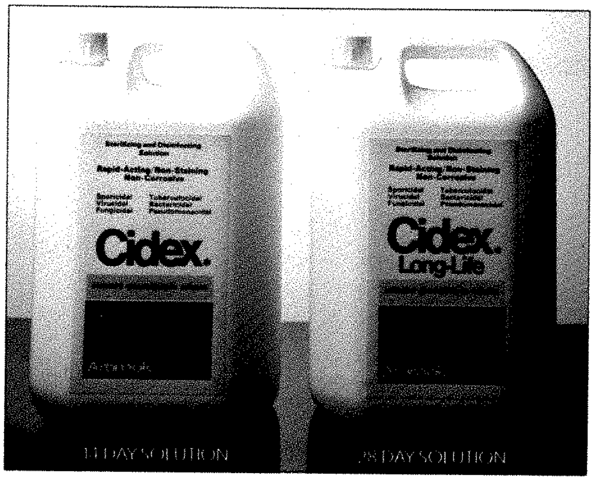

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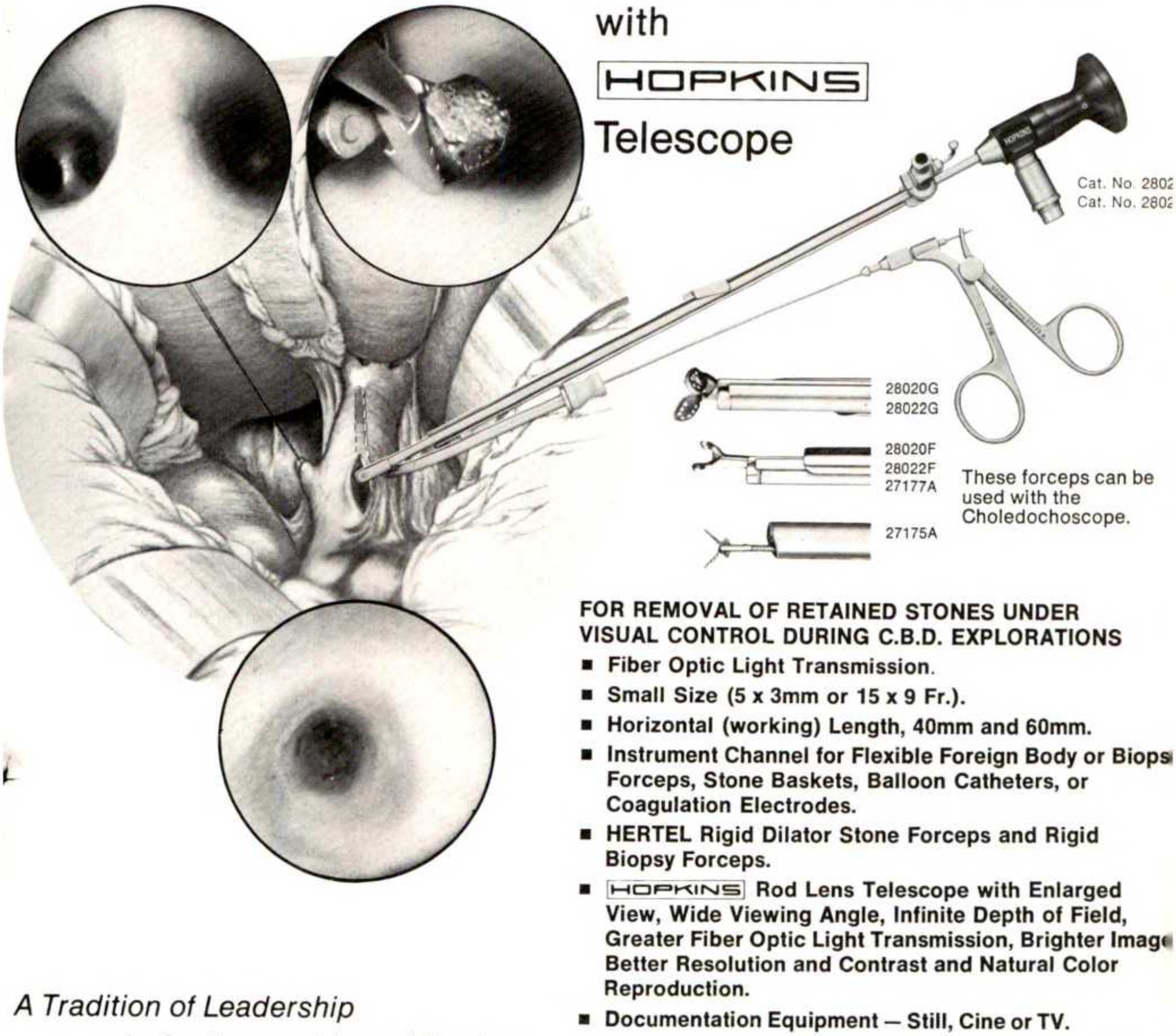

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DOSAGE AND ADMINISTRATION

The recommended dose of cisplatin in adults and children as single - agent therapy is 50 to 75 mg/m^2 as a single i v. dose every 3 to 4 weeks, or 15 to 20 mg/m^2 i.v. daily for 5 days every 3 to 4 weeks Pre - treatment hydration with 1 to 2 litres of fluid infused for 8 to 12 hours prior to a cisplatin dose is recommended Reconstitute vial contents with 10 ml of sterile water for Injection EP. The drug is then diluted in 2 litres of 5% dextrose in either 1/2 or 1/3 normal saline, (to which 37 5 g of mannitol may be added) and infused over a 6 - 8 hour period Adequate hydration and urinary output must be maintained during the following 24 hours.

A repeat course of cisplatin should not be given until the serum creatinine is below 1 5 mg/100 ml (130 μmol/l) and/or the blood urea below 55 mg/100 ml (9 mmol/l) A repeat course should not be given until circulating blood elements are at an acceptable level (platelets 100,000/mm^3, WBC 4,000/mm^3) Subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits When employed in combination with other antitumour drugs, the dose of cisplatin should be adjusted appropriately

CONTRA-INDICATIONS, WARNINGS, ETC.

Cisplatin induces nephrotoxicity, myelosuppression and ototoxicity which may be additive to pre - existing dysfunctions. Consequently, the use of cisplatin in patients with hearing or renal impairment or depressed bone marrow function may be associated with increased toxicities. Such conditions represent relative contra - indications

Cisplatin is contra - indicated in patients with a history of hypersensitivity to cisplatin or other platinum - containing compounds

WARNINGS

Cisplatin produces cumulative nephrotoxicity The serum creatinine, BUN and creatinine clearance should be measured prior to initiating therapy, and prior to each subsequent course

Anaphylactic - like reactions to cisplatin have been reported These reactions have occurred within minutes of administration to patients with prior exposure to cisplatin, and have been alleviated by administration of adrenaline, steroids and antihistamines

Safe use in pregnancy has not been established This product should not normally be administered to patients who are pregnant or to mothers who are breast feeding Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture Although carcinogenicity and teratogenicity have not been established, compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic

The influence of cisplatin on human reproduction has not been determined Cisplatin therapy might have an antifertility effect

Precautions

Cisplatin should be administered by individuals experienced in the use of antineoplastic therapy

Since renal toxicity is cumulative, measurements of BUN, serum creatinine and creatinine clearance should be performed prior to initiating therapy and prior to each subsequent dose At the recommended dosage, cisplatin should not be given more frequently than once every 3 to 4 weeks (See Adverse Reactions)

Since ototoxicity of cisplatin is cumulative, audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug (See Adverse Reactions)

Peripheral blood counts should be monitored weekly Liver function should be monitored periodically Neurological examination should also be performed regularly (See Adverse Reactions)

ADVERSE REACTIONS

Nephrotoxicity

Dose - related and cumulative renal insufficiency is the major dose - limiting toxicity of cisplatin Renal toxicity has been noted in 28 to 36% of patients treated with a single dose of 50 mg/m^2 It is first noted during the second week after a dose and is manifested by elevations in BUN and serum creatinine serum uric acid and/or a decrease in creatinine clearance

Renal toxicity, becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given.

Renal function impairment has been associated with renal tubular damage The administration of cisplatin using a 6 - 8 hour infusion with intravenous hydration and mannitol has been used to reduce nephrotoxicity However, renal toxicity still can occur after utilisation of these procedures

Ototoxicity

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4,000 to 8,000 Hz)

Decreased ability to hear normal conversational tones may occur occasionally Ototoxic effects may be more severe in children receiving cisplatin Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses It is unclear whether cisplatin - induced ototoxicity is reversible Careful monitoring of audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin.

Haematological

Myelosuppression occurs in 25 to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leucocytes occur between days 18 to 23 (range 7 5 to 45) with most patients recovering by day 39 (range 13 to 62) Leucopenia and thrombocytopenia are more pronounced at higher doses (50 mg/m^2) Anaemia (decrease in haemoglobin level by 2 g/100 ml blood) occurs at approximately the same frequency and with the same timing as leucopenia and thrombocytopenia.

Gastrointestinal

Marked nausea and vomiting occur in almost all patients treated with cisplatin, and are occasionally so severe that the drug must be discontinued Nausea and vomiting usually begin within one to four hours after treatment and last up to 24 hours. Various degrees of nausea and anorexia may persist for up to one week after treatment.

OTHER TOXICITIES

Hyperuricaemia

Hyperuricaemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid generally occur between 3 to 5 days after the dose Allopurinol therapy for hyperuricaemia effectively reduces uric acid levels

Neurotoxicity

Neurotoxicity, usually characterised by peripheral neuropathies, has occurred in some patients. Loss of taste and seizures have also been reported. Neuropathies resulting from cisplatin treatment may occur after prolonged therapy (4 to 7 months) , however, neurological symptoms have been reported to occur after a single dose.

Cisplatin therapy should be discontinued when the symptoms are first observed Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients

Anaphylactic-like Reactions

Anaphylactic - like reactions, possibly secondary to cisplatin therapy, have been occasionally reported in patients previously exposed to cisplatin The reactions consist of facial oedema, wheezing, tachycardia and hypotension within a few minutes of drug administration. All reactions may be controlled by intravenous adrenaline, corticosteroids or antihistamines Patients receiving cisplatin should be observed carefully for possible anaphylactic - like reactions and supportive equipment and medication should be available to treat such a complication

Other toxicities reported to occur infrequently are cardiac abnormalities, anorexia and elevated SGOT

PHARMACEUTICAL PRECAUTIONS

NEOPLATIN INJECTION must be stored in a refrigerator (2 C to 8 C)

EXPIRY DATE

24 months from date of manufacture

Preparation of Intravenous Solution

Dissolve NEOPLATIN with 10 ml of sterile water for injection Each ml of the resulting clear, colourless solution will contain 1 mg cisplatin

The drug is diluted in 2 litres of 5% dextrose in 1/2 or 1/3 normal saline (to which 37 5 g of mannitol may be added) and given by i v infusion over a 6 to 8 hour period.

The reconstituted solution should be protected from light, kept at room temperature and is stable for 20 hours Refrigeration will result in precipitation

LEGAL CATEGORY

POM

NEOPLATIN is available only on prescription and supplied to centres with experience in the chemotherapy of malignant disease

PACKAGE QUANTITIES

NEOPLATIN INJECTION is packed in cartons of 10 vials, each vial containing 10 mg lyophilised cis - diamminedichloroplatinum

FURTHER INFORMATION

Cisplatin has biochemical properties similar to that of bifunctional alkylating agents producing interstrand and intrastrand crosslinks in DNA. It is apparently cell - cycle non - specific Following a single i v dose, cisplatin concentrates in liver, kidneys and large and small intestines in animals and humans. Cisplatin apparently has poor penetration into the CNS

Plasma levels of radioactivity decay in a biphasic manner after an i v bolus dose of radioactive cisplatin to patients The initial plasma half - life is 25 to 49 minutes, and the post - distribution plasma half - life is 58 to 73 hours During the post - distribution phase, greater than 90% of the radioactivity in the blood is protein bound Cisplatin is excreted primarily in the urine. However, urinary excretion is incomplete with only 27 to 43% of the radioactivity being excreted within the first 5 days post - dose in human beings There are insufficient data to determine whether biliary or intestinal excretion occurs

BASIC N.H.S. COST 10mg vial £10 75

PRODUCT LICENCE NUMBER 0125/0109

DATE OF PREPARATION

January 1979

NAME AND ADDRESS

MEAD JOHNSON LABORATORIES
Division of Bristol - Myers Company Limited,
Station Road, Langley, Slough SL3 6EB   (Tel No   Slough 44266)

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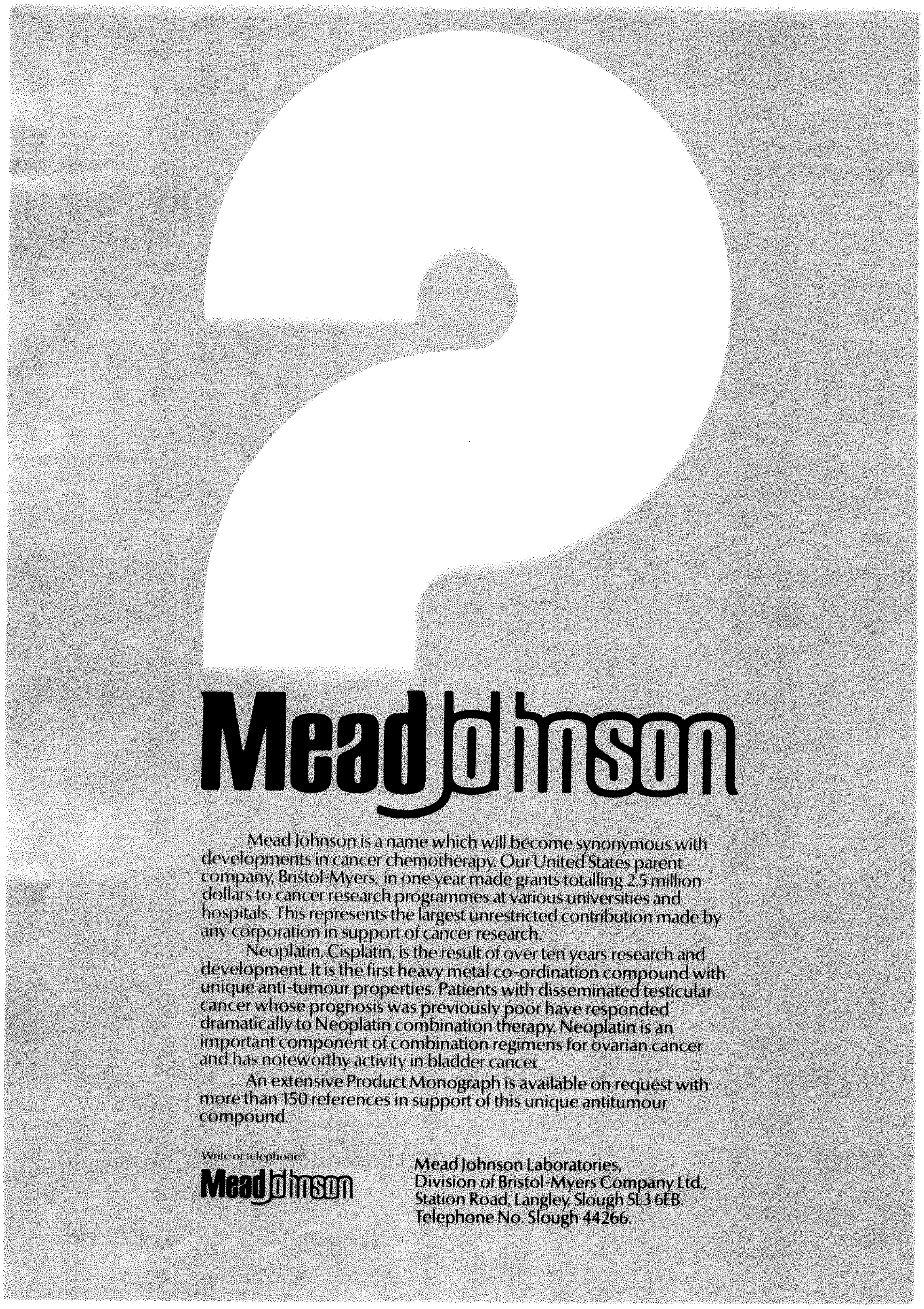

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(Cinoxacin)

Cinobac is the potent new oral therapy for chronic and acute urinary tract infections with a 96% success rate – including recurrent infections.[1]*

Cinobac combines powerful relief with a low incidence of side-effects in cystitis, pyelonephritis, pyelitis and asymptomatic bacteriuria.

A powerful antibacterial action[1]

Cinobac, a carboxylic acid derivative, is metabolised less than nalidixic acid, oxolinic acid and sulphamethoxazole, and therefore active concentrations in urine are higher than with any of these other drugs.

In the studies conducted, of all pathogens isolated in urine, less than 3% were resistant to Cinobac.

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In 26 clinical trials 1118 patients received Cinobac; investigators confirm the view that Cinobac is free from unpleasant side-effects, and is well tolerated in the treatment of urinary tract infections.[2,3,4]

Cinobac – a simple 500 mg b.d. dosage in a convenient calendar pack to aid compliance.

CINOBAC

CINOXACIN

Prescribing Information

"CINOBAC" Cinoxacin INN

Presentation

Capsules containing 500 mg cinoxacin INN PC.

Uses

CINOBAC is indicated in acute, recurrent and chronic upper and lower urinary tract infections due to susceptible micro-organisms.

Dosage & Administration

CINOBAC is administered orally. The usual adult dose is 1 g daily in two divided doses.

Contra-indications

Cinoxacin is contra-indicated in patients with a history of hypersensitivity to cinoxacin.

Warnings

The use of cinoxacin is not recommended during pregnancy, for the nursing mother, or for children as safety has not been established.

Precautions

CINOBAC is not recommended for patients with severely impaired renal function and should be used with caution in patients with reduced renal function.

Adverse Reactions

Gastro-intestinal – nausea, anorexia, vomiting, abdominal cramps and diarrhoea have been reported.

Hypersensitivity – rash, itching, urticaria and peripheral and oral oedema have occurred.

Other adverse reactions possibly related to cinoxacin include dizziness, headache, insomnia, tingling sensation, perineal burning, photophobia and tinnitus.

Transient changes in AST (SGOT), ALT (SGPT), BUN, ALP and creatinine clearance have been observed occasionally.

Basic NHS Cost ex calendar pack 68p per day.

References

1. Current Chemotherapy (Proceedings of the 10th International Congress of Chemotherapy), II, 1041. American Society for Microbiology, 1978.
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3. Proceedings of the 9th International Chemotherapy Congress, 1976, 5: 417.
4. Antimicrobial Agents and Chemotherapy, 1976, 9: 502.

*Including patients with physical abnormalities of the urinary tract.

Further information is available on request,
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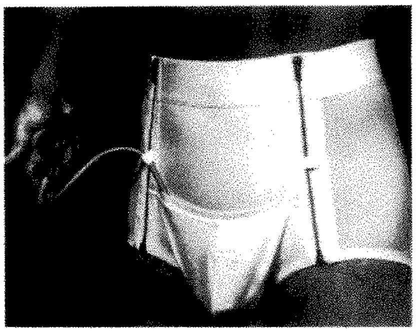

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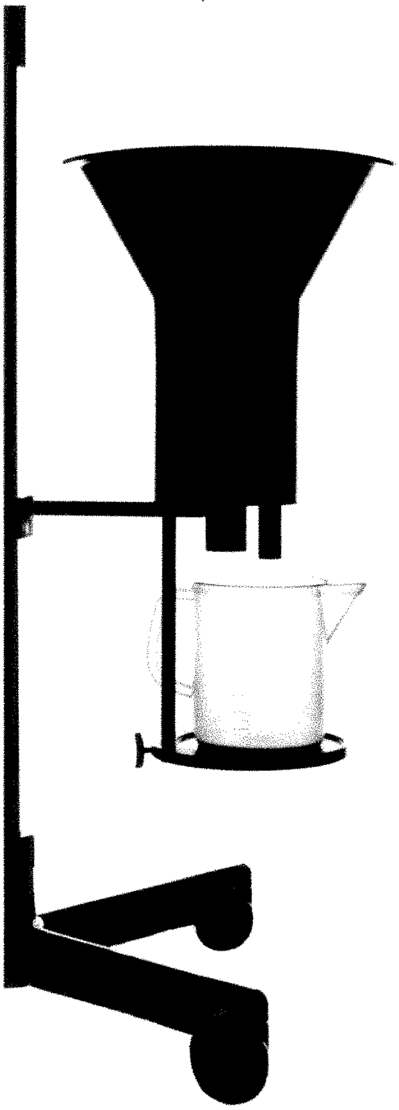

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Estracyt appears to have specific affinity for, and effect on, prostate tissue but to have only weak systemic cytotoxic effects; thus long-term administration can be tolerated.

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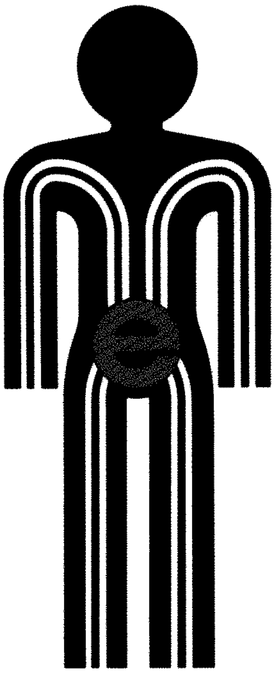
In oestrogen-resistant carcinoma of the prostate, published results of treatment of over 500 patients with Estracyt relate to 80% with Stage IV disease and 20% Stage III. They show that SUBJECTIVE response to treatment, seen in 40% to 65% of oestrogen-resistant patients,[1,2] usually occurs within 14 days, relief of pain being the most obvious benefit. OBJECTIVE responses were seen in 19%–48% of patients with advanced disease.[3,4]



Indications. Carcinoma of the prostate, especially in cases unresponsive to, or relapsing after conventional oestrogen therapy or orchidectomy.
Dosage and Administration. The adult dose ranges from 1 to 10 capsules a day by mouth, with meals. Standard starting dose 4 capsules a day with later adjustment according to response. One to 2 capsules a day may be adequate for maintenance therapy.
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Pharmaceutical Precautions. Store in cold place (2°C to 8°C).
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References
1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., 49, 73-79. 2. Mayer, E.J. Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, 32, 114-119. 3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., 111; 231-238. 4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

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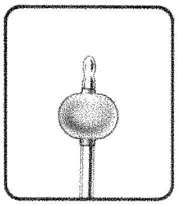

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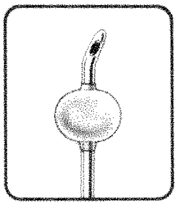

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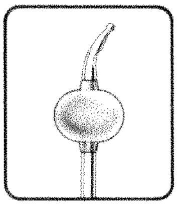

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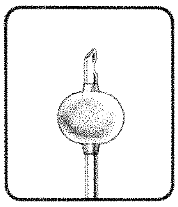

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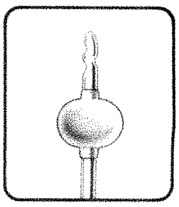

Three-way

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Comparison of Performance of Simplastic and Latex Foley Catheters

TABLE 1: *Drainage rates and Cross-sections of 2-way Catheters*

18Ch, 5ml Foleys	Average Drainage Rate	Average Cross-sectional Area of Drainage Lumen	Cross-section of Drainage Lumen as Percentage of Total Cross-section
Simplastic catheter	1,163 ml/min	12.3mm^2	47%
Latex catheter (A)	416 ml/min	5.9mm^2	24%
Latex catheter (B)	396 ml/min	5.7mm^2	23%
Latex catheter (C)	370 ml/min	4.0mm^2	17%

(Drainage rates measured under a pressure of 140mm water and with balloons inflated with 14ml water.)

TABLE 2: *Drainage and Irrigation Rates of 3-way Irrigation Foleys*

18Ch, 30ml 3-way Foleys	Average Irrigation Rate	Average Drainage Rate
Simplastic 3-way catheter	127 ml/min	466 ml/min
Latex 3-way catheter (D)	73 ml/min	277 ml/min
Latex 3-way catheter (E)	44 ml/min	171 ml/min
Latex 3-way catheter (F)	32 ml/min	350 ml/min

(Drainage and irrigation rates measured under a pressure of 140mm water with balloons uninflated.)

Tests conducted at Searle Medical Research and Development Laboratories 1978.

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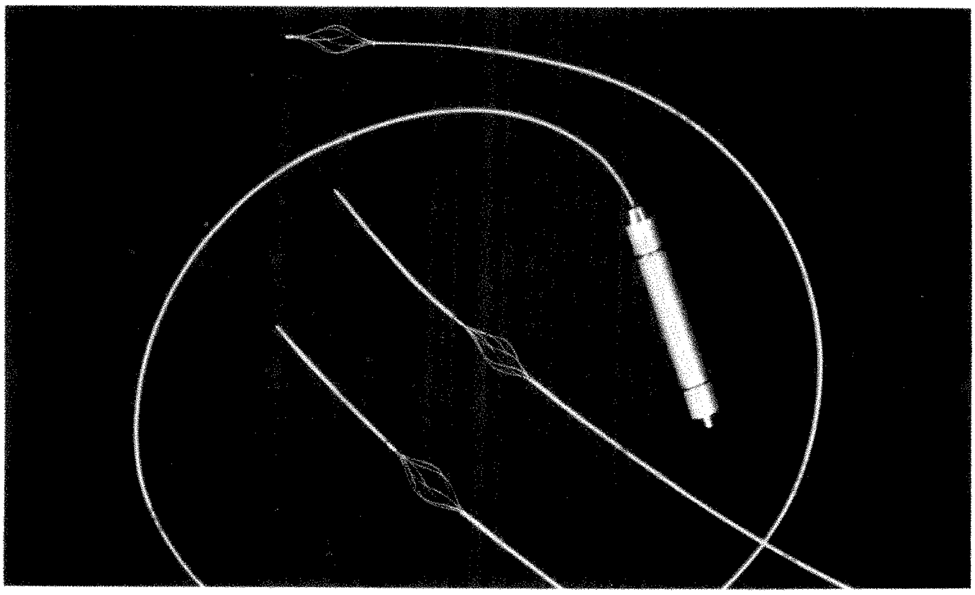

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Renal Transplantation with Multiple Arteries

M. FOX and R. YALIN

Renal Transplant Unit, Hallamshire Hospital, Sheffield

Summary—Out of a total of 184 transplant operations there were 27 kidneys with 2 or more renal arteries. Five of these were in 23 related transplants.

Ischaemic times were increased compared with those of kidneys with single arteries, but the incidence and duration of acute tubular necrosis and also the length of time spent in hospital were similar in both groups.

Excessive bleeding and other complications were no more common than following single arterial anastomosis.

Kidneys with multiple arteries can be used safely if careful interrupted suturing is performed, the kidneys are perfused before and kept cool during the procedure and polar arteries are not tied.

The incidence of multiple renal arteries has been reported to range from 20 to 30% with about equal distribution on either side (Merklin and Michels, 1958). Multiple arteries present problems to the transplant surgeon; increased technical skills are needed in the removal and vascular anastomosis, ischaemic times may be prolonged and the incidence of post-operative complications increased (Simmons *et al.*, 1971). In fact, it was common practice in the early years of transplantation to consider more than one renal artery to be a contraindication to the operation (Hume *et al.*, 1963; Murray and Harrison, 1963; Starzl, 1964). Surgical experience and improved techniques of preservation have allowed most kidneys with up to 2 separate renal arteries to be used, but reports of the incidence of post-operative complications continue to show more problems and a poorer prognosis compared with that of kidneys supplied by single arteries (Anderson *et al.*, 1972; Spanos *et al.*, 1973; Goldman *et al.*, 1975; Hall *et al.*, 1975). Our experience has been considerably more favourable than that in previously published series and it is for this reason that the results are reviewed and techniques discussed.

Patients and Methods

Out of a total of 184 transplants performed in the Sheffield Renal Transplant Unit, 27 kidneys with multiple renal arteries were transplanted, an incidence of 14.7%. Twenty-three of the total number of transplants were from living donors and 5 of these had double renal arteries, making an incidence of 22%, while the incidence of double arteries in the cadaver donors was 13.7%. The arterial configuration in the living donors was known beforehand because of arteriograms performed routinely in every case. All of the 5 related donors had bilateral multiple renal arteries. If a single vessel had been present on one side, that kidney would have been used in preference. Kidneys with arteries of roughly equal size were preferred rather than organs with one artery considerably larger than the other. In addition to the 5 related cases with double arteries, there were 2 others where the renal arteries were multiple on one side, and on the other side a very short single stem came off the aorta which then divided.

Perfusion with cold Perfudex solution was used in the initial cadaver transplants and Collins solution in the last 63 cases. The kidneys were then stored in ice, apart from 4 that were perfused in a Gambro machine. The arteries of related kidneys were injected with 500 units heparin in 2 ml normal saline immediately prior to removal. The kidneys were then transferred to the adjoining operating theatre, immersed in ice-cold saline, and kept cool by surrounding ice-cold saline packs during the operation.

The configuration of the arterial blood supply to the 27 transplanted kidneys and the techniques of anastomosis are shown in the figure. An aortic

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Accepted for publication 9 February 1979.

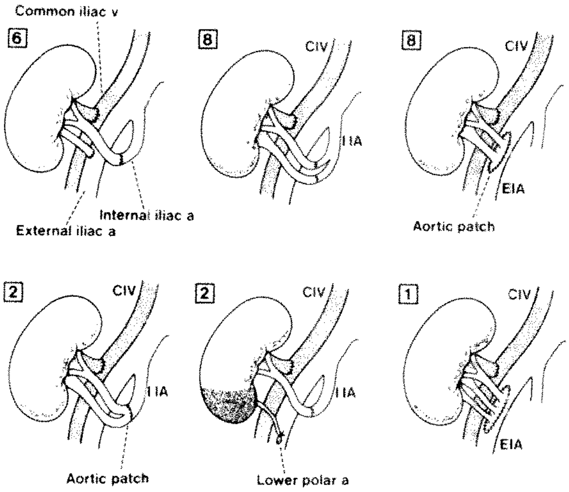

Fig. Management of multiple arteries in renal transplantation.

patch was employed in 11 cases (all cadaver donors) carrying 2 arteries in 10 instances and 3 in one case. The patch was anastomosed to the external iliac artery end-to-side in 9, and to the internal iliac artery end-to-end in 2 cases. Interrupted sutures were employed in all of the arterial anastomoses using 5/0 arterial suture (Ethiflex-Ethicon Ltd). The 2 main branches of the internal iliac artery were mobilised and anastomosed individually end-to-end in 8 patients. In 6 cases end-to-end anastomosis to the internal iliac artery of one renal artery and end-to-side anastomosis to the external iliac artery of the other artery were performed. A very small lower pole artery was ligated in 2 donor kidneys.

The period of time it took to perform the anastomoses, both arterial and venous, is shown in Table 1. A single venous anastomosis (end-to-side) to the common iliac vein was performed in all but one patient who had 2 veins almost equal in size. The veins were sutured together first and then anastomosed also as one, end-to-side to the common iliac vein. If one or more small veins were present they were ligated. The anastomosis times required in all cases, whether cadaver or related in origin, tended to be longer than when single arteries were employed but the differences were small.

Table 1 Relation of Anastomosis Time to Number of Renal Arteries

	Arteries	*Number*	*Anastomosis time (min)*
Cadaver	Single	139	32 (20-95)
	Multiple	22	43 (29-62)
Related	Single	18	32 (23-47)
	Multiple	5	39 (37-47)

The incidence of post-operative acute tubular shutdown, number of dialyses required, number of rejection episodes and length of time in hospital are compared in Table 2. Only related transplants could be compared satisfactorily in this manner because of variable factors such as pre-operative hypotension and ischaemia in those from cadavers. The period of time spent in hospital was almost the same in the 2 groups. Operations involving more than one arterial anastomosis were technically more difficult than when single vessels were present. This was reflected in the increased time taken to complete the anastomosis. The kidneys were kept cool during this period but the marginal increase in cold ischaemic time made no difference to the incidence or duration of acute tubular necrosis compared with kidneys which required a single arterial anastomosis. A total of 11 rejection episodes occurred in the group of 18 related patients with single vessels in the first 30 days (61%) compared with 5 rejections in 5 patients with double arteries. The difference between the 2 groups was not statistically significant.

There was no operative mortality associated with any of the multiple artery transplants. All 5 related transplant recipients are alive between 5 months and 7½ years after operation with well functioning kidneys. Eleven patients who had received cadaver kidneys with multiple arteries are living after 1 to 9 years with functioning kidneys, and a further 5 have had transplant nephrectomies because of rejection. Four have died; 2 of these were children aged 8 and 12 years, both of whom died within one month of surgery, one after early rejection, the other due to renal vein thrombosis and sepsis. Immunological rejection associated with pancreatitis and cardiac failure was the cause of death in the third, while the fourth patient rejected his kidney after one year and then died one month after the second cadaver transplant from rejection and infarction of a renal pole following ligation of a small artery supplying that area.

Table 3 shows the incidence of some other problems encountered in these patients.

Double arterial anastomoses gave a higher incidence of per-operative bleeding in cadaver trans-

Table 2 Related Transplants

Arteries	*Number*	*Post-op acute tubular necrosis*	*Rejection episodes (within 30 days)*	*Serum creatinine (at 30 days)*	*Hospital stay (days)*
Single	18	2	11	170 (80-500)	33 (16-90)
Multiple	5	1	5	120 (60-240)	35 (14-53)

plants—4/22 (18%) compared with 12/139 (7%) in transplants with single arteries, but in all cases the haemorrhage was controlled with additional interrupted sutures. There was no reactionary or secondary bleeding, apart from one patient with multiple renal arteries who needed evacuation of residual haematoma. Two cases were technically difficult because of the small size of a polar artery. The small artery was gently dilated with a probe and then with "mosquito" artery forceps, and anastomosed by means of 4 corner 5/0 Ethiflex sutures end-to-side to the external iliac artery. One of these 2 arteries thrombosed. In the patient who had had a small upper polar artery tied, necrosis developed in the segment supplied and a urinary fistula formed. Partial nephrectomy with formal closure of the major upper calix was performed with subsequent recovery. A fistula from a localised area of necrosis in the renal pelvis occurred in one patient who had received a kidney from a relative with a double arterial supply. There was no impairment of the blood supply of the renal substance; the exact cause was never found but a localised diathermy burn could have been responsible. At open exploration the edges of the small opening in the renal pelvis were approximated with 4/0 chromic catgut sutures and a piece of greater omentum was brought out of the peritoneum and sutured over the renal pelvis. Leakage continued for another 34 days, after which the patient made a full recovery.

Distal ureteric necrosis with resulting fistula formation occurred in 2 patients, one with a double and the other with a single arterial supply. The incidence of other lower urinary tract fistulae was higher in patients with single arteries. There was no incidence of renal artery stenosis in any of the cases with multiple arteries and no problems occurred with infection. Mortality within one month of operation was compared in the 2 groups. The overall death rate was 5.4% in that period. There was no increase in patients who had received kidneys with multiple arteries.

Discussion

Donor kidneys with double arteries can be used satisfactorily and this anatomical variation is not a contraindication to transplantation from either a living or a cadaver donor. If more than 2 vessels are present in a cadaver donor, provided that a Carrel patch can be taken from the aorta to make, at the most, a double anastomosis, the procedure should be safe. Ligation of a small polar artery has been advocated (Spanos *et al.*, 1973), but from our experience and that of others the procedure is unsafe because of the danger of localised sloughing and fistula, hypertension, infection and rejection (Smith *et al.*, 1962; Spanos *et al.*, 1973; Goldman *et al.*, 1975). If the vessels appear too narrow or have been cut too short, partial nephrectomy may be required, but it is useful to inject methylene blue to outline the

Table 3

	Multiple arteries		*Single arteries*	
	Cadaver (22)	*Living* (5)	*Cadaver* (139)	*Living* (18)
Excessive bleeding at time of surgery	4	—	12	—
Haematoma requiring evacuation	—	1	—	—
Upper urinary tract fistula	1	1	—	—
Distal ureteric necrosis (fistula)	1	—	—	1
Lower urinary tract fistula	—	1	20	3
Mortality within 1 month	1	—	8	1

exact extent of the ischaemic area. A lower polar branch can supply also the renal pelvis and ureter, and every attempt should thus be made to re-establish the blood supply. Microsurgical techniques have been reported as helpful (Merkel *et al.*, 1976) and interposition of an arterial or venous graft have been used (Belzer *et al.*, 1972). The advantages of side-to-side arterioplasty performed at leisure *in vitro* after removal of the kidney during the period of cold ischaemia, with eventual single *in vivo* anastomoses, have been advocated (Belzer *et al.*, 1972; Codd *et al.*, 1974; Vineyard and Tilney, 1976). The final single anastomosis is then easier to perform without prolongation of the warm ischaemic time. However, the results in the present series have shown no increase in problems or incidence of acute tubular necrosis as a result of the relatively small extension of time required to complete the additional anastomosis which can, if necessary, be performed after re-establishing the circulation in the major vessel.

An increased incidence of serious haemorrhage has been described by Mosley and Castro (1978) following end-to-side anastomosis to the external iliac artery, whether or not a patch has been used, if rejection occurred later. This has not been our experience, apart from one 22-year-old patient who had had an arterial patch on his external iliac artery and who bled profusely from the anastomosis site following acute rejection. Emergency ligation of the external iliac artery above and below the anastomosis was required. After 6 months, complete compensation of arterial supply to the affected limb occurred. Proximal and distal ligation can be performed safely in a young person in an emergency, a finding observed as long ago as 1813 by Astley Cooper. However, it is best not to invite this situation and to use an end-to-end anastomosis to the internal iliac artery if at all possible. A donor arterial patch can also be fashioned on to the internal iliac artery relatively easily.

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The Frequency of Renal Stones within Great Britain in a Gouty and Non-gouty Population

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Summary—In a general practice survey carried out during 1976, the incidence of renal stones was found to be 82/100,000. When this population was divided into gouty and non-gouty subjects, the incidence of stones was found to be 870/100,000 and 79/100,000 respectively. Only 28% of the stone patients were found to have a chronic condition, including hyperuricaemia, which might predispose towards stone disease.

In the population of 604 gout patients, 37 were found to have renal stones. These patients were diagnosed later than the average gout patient and also had a higher incidence of other chronic conditions.

Anderson (1964) found an annual hospital admission rate for urinary tract stones of 69 patients per 100,000 population in the Outer Hebrides. From a sample of hospital in-patient enquiry data, Barker and Donnan (1978) calculated the average annual discharge rates per 100,000 for renal and ureteric stones and renal and ureteric colic, combined, to be 48.7 for England and Wales. Both of these incidence figures are markedly less than the 1% incidence quoted by Williams (1966) for urinary tract stones in the general population of Great Britain. An Australian survey (Bennett and Hughes, 1972) found an average annual incidence of renal stones among hospital admissions of 697 per 100,000 (223 of 31,994 patients) and Andersen (1969) states that the incidence in Caucasian countries is of the order of 400 to 800 per 100,000 admissions. In a leading article in the British Medical Journal (1965), the incidence of urinary stones among hospital admissions was quoted as ranging from 19 to 193 per 100,000, while the incidence from autopsy cases in 2 different centres in the USA was 1.1% of 24,561 and 1.3% of 5,900 (1,100 and 1,300 per 100,000 respectively). The recurrence rate following an initial attack is high (Sutherland, 1954; Marshall *et al.*, 1975) and may even reach 60 to 80% (Williams, 1963; Mathew, 1974).

Data about recurrence rates are often conflicting and may appear to vary considerably from centre to centre. This may reflect the number of patients seen and the length of time of follow-up as well as environmental factors such as weather and diet.

It has been noted that gout patients suffer from renal stones more frequently than the general population (Gutman and Yu, 1968; Cameron, 1973), and Wyngaarden and Kelley (1976) state the incidence of renal stones in gouty patients as being at least 1000 times that of the general population.

While a guide to incidence can be taken from the recent literature quoted above, it is largely based on specific subgroups of the population, for example autopsy cases and hospital admissions. However, relatively little data are available which would relate to general practice in Great Britain today. The number of episodes of stones per year for the total population is given as 80 per 100,000 (*Morbidity Statistics from General Practice*, 1974).

In the present study, the incidence and prevalence of renal stones in normal and gouty subjects has been determined by means of general practice questionnaires.

Methods

During 1977, 17 practices, each with a diagnostic recording index system and consisting of 27 general practitioner patient lists and a combined patient population of 64,454, agreed to provide details on all patients who were diagnosed as

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having had a clinical episode due to renal stone during 1976. As well as patient age and sex, information was requested on the type of attack, whether a stone or gravel was passed, or if the patient had had an episode of typical colic, which investigations had been undertaken, the number of episodes of stone or colic before 1976, the year of first incidence of stone or colic, whether the patient had been referred to hospital, and what other chronic conditions predisposing to renal stone formation were present.

Further information was also collected from these 17 practices and 47 others with a diagnostic index and a total patient population of 374,832. A full description of the method has been published elsewhere (Currie, 1979). In 604 cases of gout, diagnosed clinically and confirmed by a raised urate, information was obtained on the presence of renal stones, the age, sex, weight, family history of gout, and personality assessment. In addition, information was collected on the time interval between first clinical presentation and diagnosis of gout, the presence of associated chronic conditions, the use of interval therapy and whether the diagnosis was made by the practice or by hospital.

All results have been analysed by the chi-squared (χ^2) test with Yates correction. Where a cell size was less than 5, Fisher's exact test was used.

Results

Incidence of Renal Stones in 1976

Out of a total study population of 64,454 patients, 53 reported a total of 67 stone episodes during 1976. Data on these patients are given in Table 1. The average number of stone episodes per year per general practitioner list was 2.5 (range 0-3).

Table 1 Analysis of the Study Population With Respect to Renal Stone Disease

Characteristic	*Number*
Total study population	64,454
Total number of stone patients	53
Number with gout	2
Total number having first attack in 1976	20
Number of males	35
Mean age years (range)	49.7 (10-74)
Number of females	18
Mean age years (range)	46.5 (21-65)
Number of patients with more than 1 episode in 1976	11 (6 male, 5 female)
Number of patients with more than 2 episodes in 1976	3 (2 male, 1 female)

From the data presented, it can be seen that relating to 1976, the overall incidence of patients with renal stones was 82/100,000 population, and the incidence of episodes was 104/100,000 population. The 17 practices studied had an indexed population of 224 gout patients, 2 of whom had stones; this gives an incidence of renal stones in the gout population of 890/100,000 gout patients, but numbers are too small to permit firm comment. The incidence in the non-gout population of 64,230 was 79/100,000 population.

Of the 53 patients experiencing stone episodes in 1976, 33 had had one or more episodes of stone recorded in their diagnostic index in previous years and 10 of these had more than one episode in 1976 Of the 20 patients presenting with their first ever episode of renal stone or colic in 1976, one had a further episode that year. In these 34 recurrent stone formers, at least 88 stones were known to have been passed previously, and the mean duration of stone disease was 7.8 years. From this it can be calculated that in 1976, the incidence of new stone formers was 31/100,000 and the incidence of recurrence was 53/100,000 population.

Classification of Type of Attack

There were found to be 9 episodes of stone passage, 2 where the stone was removed surgically, 17 where it was visualised by X-ray examination, 55 episodes of colic, and 8 of gravel. In only one case was stone analysis done, but 35 patients had X-ray examination, 30 had blood tests and 50 urine examination.

Factors Predisposing to Renal Stones

Fifteen (28%) of the 53 patients having a stone episode in 1976 also had some other chronic condition which might predispose toward stone

Table 2 Possible Causes of Lithiasis in 53 Stone Formers

Hyperuricaemia	5 (♂)
Gout (also had hyperuricaemia)	2 (♂)
Recurrent urinary tract infection	6 (3♂, 3♀)
Vitamin D/calcium excess	1 (♀)
Hyperparathyroidism	1 (♀)
Cystinuria	1 (♂)
No cause given	38

formation (Table 2). The remaining 38 (72%) of the patients had no obvious aetiological factors.

Referral to Hospital

Of the total 53 patients, 43 (81%) were investigated in hospital for their stones, but of the 11 patients having more than one stone episode during the year, only 2 attended hospital on more than one occasion, and one did not attend on any occasion. Fifteen patients (28%) entered hospital for assessment for possible surgery.

Prevalence of Renal Stones in 604 Gout Cases

From the extended study group of 64 practices, enquiries among 604 gout patients as at December 1975 into the clinical presence or absence of renal stones revealed 37 to be so afflicted, giving a prevalence of 6130 per 100,000 gout patients.

A Comparison of Gout Cases With and Without Recognised Renal Stones

A comparison of those with and without recognised renal stones within this group of 604 gout patients showed them to be comparable for age, sex, weight and a family history of gout. However, some differences were noted. Using a 7-point personality scale covering introversion to extroversion, it was found that the renal stone patients fell more into the introvert class (significant at the 5% level). When the stone and non-stone groups were studied with respect to the time lag between the clinical appearance and diagnosis of gout, only 22 (59%) of the 37 stone patients, but 470 (90%) of the 520 non-stone patients, were diagnosed within 2 years. This difference is significant at the 0.1% level and is interesting since in 22 of the 37 stone patients this condition preceded the appearance of clinical gouty arthritis.

In relation to the associated conditions listed in Table 3, the stone group had a significantly higher association with angina pectoris (1% level), myocardial infarction (0.1% level), renal damage (0.1% level), hypertension (1% level) and diabetes mellitus (1% level). Equally, when all the associated conditions (Table 3) were added together, the stone group had a significantly greater association at the 1% level.

There was no significant difference in the current gout therapy of the 2 groups; 62% of the stone patients, as compared with 44% of the non-stone patients, were receiving interval therapy. Equally, the difference in the hospital diagnosis rate, being 14% in the stone group and 7% in the non-stone group, did not reach statistical significance.

Discussion

The finding that of the 53 patients who were stone formers, 33 (62%) had been diagnosed in a previous year as having a renal stone, is in agreement with data from Mathew (1974) who reported recurrences in 60 to 80% of patients over a 10-year period and Blacklock (1969) who found a 67% recurrence. However, the incidence of recurrent stones is greatly affected by the duration of the follow-up period. In the patients with recurrent stones in this study, the mean duration of stone disease was 7.8 years, which compares well with the 10-year follow-up mentioned above.

Of the 53 stone patients, 43 were investigated in hospital but only 15 entered hospital and therefore would be represented in hospital discharge rates, giving a frequency of renal stones of 23/100,000 population. As stated in the introduction, Barker and Donnan (1978), in their recent study of hospital discharge statistics, found the incidence of renal stones plus colic to be 48.7/100,000 population per year. However, as they pointed out, patients with renal stones are liable to repeated

Table 3 Analysis of Associated Diseases in Gouty Patients With and Without Renal Stones

Associated condition / *Patient group*	*Cerebrovascular disease*	*Angina*	*Myocardial infarction*	*Congestive heart failure*	*Peripheral vascular disease*	*Renal parenchymal*	*Hypertension*	*Diabetes*	*Hypothyroidism*
37 renal stone patients with gout	4 10.8%	11 29.7%	10 27.0%	6 16.2%	4 10.8%	5 13.5%	18 48.6%	4 10.8%	1 2.7%
567 gout patients without stone disease	41 7.2%	74 13.0%	41 7.2%	74 13.1%	36 6.3%	8 1.4%	150 26.4%	9 1.6%	6 1.1%

admission due not only to repeated attacks but also to discharge and subsequent readmission in relation to the same attack. Nevertheless, even ignoring such factors, their quoted incidence is only 59% of the incidence of 82/100,000 found in the present study. However, as this study shows, not all patients diagnosed as having a renal stone are referred to hospital and of those referred, only 35% (15 of 43) were admitted and thus able to be incorporated in the hospital in-patient statistics. If hospital discharge rates tend to give a low frequency of stone disease, autopsy records show that there is a far higher frequency of stone disease. This probably reflects the number of patients with asymptomatic stones as well as bias due to selection. Incidences of stone disease obtained from general practice surveys would be expected to lie between hospital discharge rates and autopsy findings, and this has been found to be so in the present study.

While in the present study just over 6% of 604 gout patients had renal stones, Gutman and Yu (1968) found 22% in their series of 1394 cases, which is 3.4-fold greater. However, their patients were differently selected, being in a specialist hospital clinic. Certainly in a recent report, the stone prevalence in hospital referred gout cases in Great Britain was twice that among those gout patients not referred (Currie, 1978).

Moreover, data collected in recent years will probably reflect changes in the treatment of gout, particularly the introduction of allopurinol, which will tend to reduce stone formation. While an analysis of content of the stones in the gout cases is not available, the higher frequency of renal stone formation in this group would be due not only to the production of uric acid stones, but also to those of calcium oxalate. It is thought that calcium containing stones occur more frequently because uric acid may act as a contributory factor in their formation, with a uric acid crystal acting as a nucleus (Lonsdale, 1968; Pak and Arnold, 1975) or by the urate ions causing calcium oxalate to salt out (Tscharnke and Unger, 1973; Kallistratos, 1974) or alternatively by uric acid reducing the action of acid mucopolysaccharides in inhibiting crystal formation (Robertson, 1976) in the urinary tract.

From a comparison of the profiles of the gout patient without renal stones and the gout patient with renal stones, it can be seen that while there are many similarities between the groups, there are also some noticeable differences, the most striking being the significantly greater association of vascular disease in the renal stone group.

No clear picture arises from which it would be possible to predict which gout patient will eventually develop renal stones or in which patient presenting with renal stones is this the first symptom of gout. However, the results suggest that the patient presenting with renal stones before the onset of typical gouty articular symptoms, but who is eventually diagnosed as having gouty arthritis, will have a greater likelihood of having other chronic conditions than the average gout patient. This may be related to a more marked urate disturbance or to the presence of renal damage and its association with hypertension and resultant associated sequelae.

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The Composition of Urinary Stones in the Sudan

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Summary—Seventy-eight urinary stones from the Sudan were analysed quantitatively; 75.6% of upper urinary tract (UUT) stones and 37.8% of lower tract (LUT) stones were composed of pure calcium oxalate monohydrate.

The composition of adult UUT stones in the Sudan is almost identical to that of similar stones from Leeds except that the former contain much more calcium oxalate and much less calcium phosphate.

A smaller proportion of adult LUT stones from the Sudan contain magnesium ammonium phosphate and a larger proportion contain uric acid/urate than similar stones from Leeds.

Juvenile LUT stones from the Sudan probably contain more calcium oxalate and less uric acid/urate than juvenile bladder stones in some other developing countries.

Investigations indicate that urinary stones in the developing countries differ in composition from those found in the industrialised countries (Lonsdale *et al.*, 1968). This study describes the composition of urinary stones in the Sudan and compares it with that of stones in Leeds (England) and in some developing countries.

Materials and Methods

All stones were derived from patients treated in the Urology Department of Khartoum North Hospital, Sudan. The patients came from different parts of the country, mostly from rural areas. All social classes were included.

Seventy-eight stones were analysed quantitatively by the method of Hodgkinson (1971).

Any compound which constituted less than 10% of the weight of the stone was disregarded.

Results

The results of analysis of stones from the Sudan and comparison with stones from Leeds are shown in Tables 1 and 2 respectively.

It was found that 75.6% of upper urinary tract stones were composed of pure calcium oxalate. Another 12.2% were composed chiefly of calcium oxalate but they also contained 10 to 20% of calcium phosphate (hydroxy apatite). There were no pure calcium phosphate stones; 4.8% were composed of magnesium ammonium phosphate (MAP) with calcium phosphate, and 7.2% were uric acid stones with or without calcium oxalate. With the exception of one stone, which was composed mainly of uric acid, none of our UUT stones contained acid ammonium urate (AAU), even in trace amounts.

Discussion

Comparison between adult upper urinary tract stones in the Sudan and in Leeds indicates that the composition of the 2 groups is identical except that pure calcium oxalate stones are twice as common in the Sudan as in Leeds. Otherwise our findings agree with the observations made by Sutor (1976) that adult UUT stones in developing countries have the same composition as those in industrialised countries.

Nine UUT stones were analysed from children under 16 years of age. In this small number there was little difference between the composition of adult and juvenile UUT stones, 75% of the former and 78% of the latter being pure calcium oxalate. This is quite different from the composition of juvenile UUT stones in the United Kingdom, where phosphate was found to be the predominant constituent (Myers, 1957; Gaches *et al.*, 1975). Only one of our juvenile UUT stones contained calcium phosphate.

Sutor (1976) noted that uric acid was the major constituent of adult LUT stones in some develop-

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Table 1 Composition of Stones from the Sudan

	Upper tract stones						*Lower tract stones*			
	Sex		*Age*		*All patients*		*Age*		*All patients*	
	M	*F*	*Adult*	*Child*	*No.*	*(%)*	*Adult*	*Child*	*No.*	*(%)*
Calcium oxalate	23	8	24	7	31	75.6	9	5	14	37.8
Calcium oxalate + calcium phosphate	4	1	4	1	5	12.2	0	0	0	-
Uric acid	1	0	1	0	1	2.4	2	1	3	8.1
Urate	0	0	0	0	0	-	0	1	1	2.7
Calcium oxalate + uric acid	1	1	1	1	2	4.8	0	0	0	-
Calcium oxalate + urate	0	0	0	0	0	-	4	7	11	29.7
MAP	0	0	0	0	0	-	3	0	3	8.1
MAP + calcium phosphate	2	0	2	0	2	4.8	0	0	0	-
MAP + calcium oxalate + calcium phosphate	0	0	0	0	0	-	2	1	3	8.1
MAP—urate—calcium phosphate	0	0	0	0	0	-	0	1	1	2.7
Cystine	0	0	0	0	0	-	1	0	1	2.7
Total no. of stones	31	10	32	9	41	-	21	16	37	

MAP = Magnesium ammonium phosphate.
Children = Under the age of 16 years.

Table 2 Comparison of the Composition of Adult Stones in the Sudan and Leeds

Upper tract stones

	Sudan		*Leeds* (Hodgkinson and Nordin, 1976)	
Calcium oxalate	75%	87.5%	34.4%	86.6%
Calcium phosphate	0		7.6%	
Calcium oxalate + calcium phosphate	12.5%		44.6%	
MAP	0	6.3%	7.0%	7.0%
MAP + calcium phosphate	6.3%		0	
Uric acid	3.2%	6.4%	5.1%	5.1%
Uric acid + calcium oxalate	3.2%		0	
Cystine	0		1.2%	
Number of stones	32		157	

Lower tract stones

	Sudan	*Leeds* (Nordin and Hodgkinson, 1967)
Calcium oxalate and/or calcium phosphate	42.9%	43%
MAP with or without calcium	23.8%	57%
Uric acid/urate with or without calcium	28.5%	0
Cystine	4.8%	0
Number of stones	21	26

MAP = Magnesium ammonium phosphate.

ing countries, with smaller amounts of oxalate, urate and phosphate. In the Sudan 42.9% of LUT stones were pure calcium oxalate and this is the major constituent. Uric acid was present in only 9.5% of adult LUT stones and these were pure uric acid stones. Data from developing countries refer mostly to juvenile LUT stones analysed qualitatively. Although it may be difficult to compare the results obtained by these methods with quantitative results, it seems that more Sudanese juvenile LUT stones contain oxalate and fewer contain uric acid urate than similar stones from developing countries. Table 1 shows that of 16 juvenile LUT stones 31.3% were pure calcium oxalate and calcium oxalate was present in 81.4%; 12.6% of our juvenile LUT stones were pure uric acid or urate and this was present in 62.7%. In contrast, only 4% of juvenile LUT stones from Thailand were pure calcium oxalate. The commonest constituent in Thailand was uric acid/urate, which occurred in 82% (Greshoff *et al.*, 1963). In Turkey 36% of juvenile bladder stones were composed of pure uric acid and 14% of pure calcium oxalate (Eckstein, 1961). In India all juvenile bladder stones were found to contain uric acid (Ramalingaswami and Aurora, 1961). In Egypt calcium oxalate was found to occur in 58% and uric acid in 55% of juvenile bladder stones (Loutfi *et al.*, 1974).

The increase in the oxalate content and decrease in the uric acid/urate content of LUT stones are considered to be possible signs of change towards the composition of similar stones in industrialised countries as a result of improved socio-economic conditions (Anderson, 1969; Sutor, 1976). Our data indicate that, if this statement is correct, the Sudan lies in an intermediate position between these developing countries and the industrialised countries. This is supported by our findings that over the last 40 years UUT stones are becoming progressively more frequent than lower tract calculi.

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Hydatid Cyst of the Kidney: 8 Cases

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Summary—The clinical features, investigations and treatment of 8 patients with renal hydatid disease are presented. It is stressed that this condition is a rare differential diagnosis of space-occupying kidney lesions and diagnosis depends mainly upon radiological evaluation. Of the laboratory tests that suggested infestation eosinophilia was the most reliable. When partial nephrectomy was carried out or when there was the danger of rupture of the cyst during the operation, preliminary instillation of 2% formalin into the cyst was always done.

Renal hydatid disease is an uncommon condition whose clinical manifestations are sometimes difficult to distinguish from those of other types of urinary tract lesion, and it is difficult to diagnose accurately because the disease is often forgotten as a differential diagnosis.

Echinococcosis is globally widespread but there are several countries in which its presence is endemic. In Portugal, the province of the Alentejo is most affected by this disease because of its low socio-economic conditions, and also because dogs and sheep can roam freely on large stretches of farmland, so that control of the disease is ineffective.

The infrequency with which hydatid parasites settle in the genitourinary tract is due to the existence of hepatic and pulmonary filters which trap most of the ingested parasites, so that only about 10% reach the kidneys and other urinary organs (Fuloria *et al.*, 1975). When infestation of the genitourinary tract does take place, the most commonly affected organ is the kidney, but sometimes secondary involvement from infestation in adjacent viscera can occur (Kirkland, 1966).

Patients and Methods

In the past 18 years, 28,332 urological patients have attended São José Hospital and Curry Cabral Hospital in Lisbon, and of these only 8 were diagnosed as suffering from renal hydatid disease. Their ages ranged from 17 to 76 years; 5 patients were male and 6 lived in the Alentejo. The left kidney was affected in 5 patients and the right kidney in the remaining 3. No cases of bilateral involvement were encountered.

Clinical Features

In one case the renal hydatid cyst was accidentally discovered during investigation for arterial hypertension. In 3 other cases the cysts were associated with either an infection or the appearance of scolices or daughter cysts in the urine. Persistent, dull back pain or renal colic, dysuria with frequency, and the passage of cloudy purulent and bloodstained urine were observed in all but one case. Fever was present in 2 cases.

The passage of hydatid material in the urine was usually accompanied by severe ureteric colic and in one of our cases episodes of abdominal pain led to the diagnosis of acute appendicitis with subsequent operation.

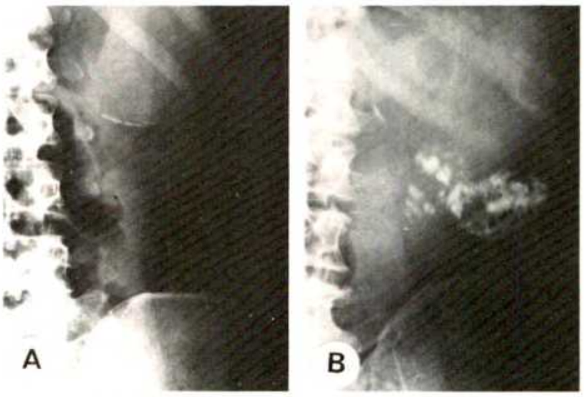

Fig. 1 (a) Curved calcification outlining enlarged upper part of left kidney. (b) Enlarged left renal shadow and heterogeneous calcification.

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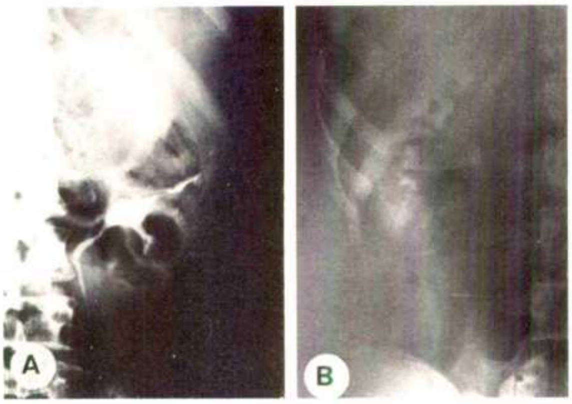

Fig. 2 *Excretion urogram:* (a) Space-occupying lesion exerting downward pressure on calices and pelvis. (b) Lower calices unclear. Hypertransparency of lower pole. Lacune of pelvis and lower calices.

Changes in the general health of one patient included weight loss, anorexia and asthenia.

Abominal examination usually revealed an enlarged kidney which was painful in 5 patients, but in one patient there was a mass with cyst-like features of the inferior pole of the left kidney.

Laboratory Investigations

Anaemia and increased erythrocyte sedimentation rate occurred in 4 patients; leucocytosis with eosinophilia ranging from 8 to 16% was found in 6 patients. Casoni and Weinberg reactions were carried out on 6 patients. The Weinberg reaction was always negative and the Casoni test was positive in only one patient. Proteinuria ranged from a trace in 5 cases to 2 g/24 h in one patient. Haematuria occurred in 2 of 3 patients in whom the passage of hydatid parasites into the urine was present, and in one case in which this did not occur.

Investigations

Chest X-rays showed no evidence of pulmonary hydatid disease but plain abdominal X-rays showed abnormalities such as renal enlargement, calcification which outlined hydatid cysts and heterogeneous calcification (Figs. 1a and b).

Excretion urography usually showed a space-occupying lesion in the kidney (Fig. 2a), but sometimes a cyst was outlined within the pelvicaliceal system (Fig. 2b). In 3 patients the kidney did not visualise on urography, and in another there was impaired function. Retrograde pyelography on 5 patients demonstrated stretched, flattened and irregular calices (Figs. 3a and b) and extravasation of contrast medium occurred in 2 patients (Fig. 3c). The ureter was occasionally seen on retrograde pyelography to be displaced and obstructed.

Selective renal arteriography in 5 cases confirmed the presence of an avascular space-occupying lesion and this examination also defined the extent of normal renal parenchyma related to the cyst (Fig. 4).

Ultrasonography was carried out on only one

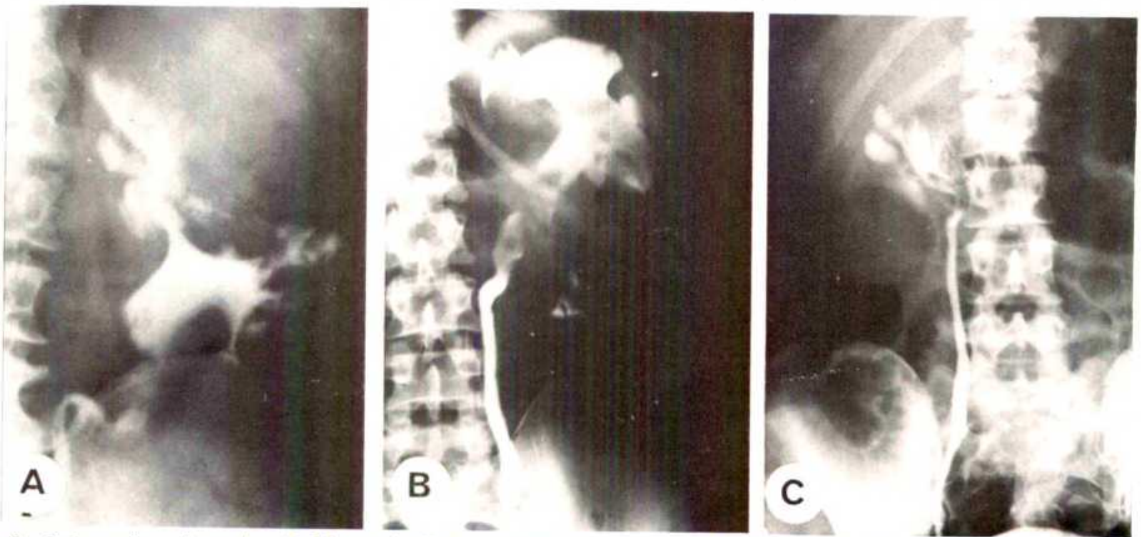

Fig. 3 *Retrograde pyelography:* (a) Distorted calices. Irregularities in pelvis and lumbar ureter. Intramembranal extravasation of contrast. (b) Calices distorted and dilated by large lesion. (c) Crushed, dwarfed pelvis and caliceal dilatation. Intramembrane contrast extravasation.

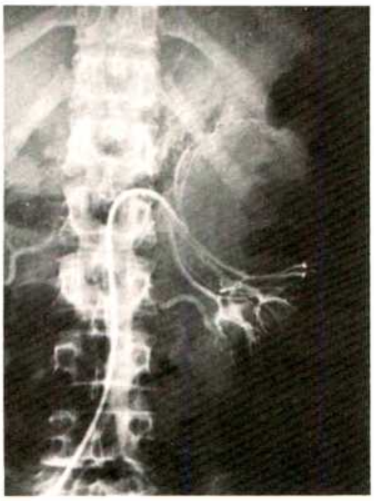

Fig. 4 *Arteriography:* Upper pole exhibiting circular, avascular lesion.

patient and this confirmed the presence of a cystic space-occupying lesion.

Treatment

Six patients underwent nephrectomy without prior formalinisation, so that large cysts that had either destroyed or infected the kidney were removed. Excision of a cyst, including removal of the adventitia, was unsuccessful in one patient because a fistula was present and this was thought to have been caused by prior injection of 2% formalin into the cyst (Matos Ferreira *et al.*, 1969). In another patient (Figs. 1a, 2a and 4), complete excision of a cyst was carried out after instillation of a 2% solution of formalin and this was probably successful because the cyst did not communicate, as in the former case, with the pelvicaliceal system.

Discussion

Although hydatid disease of the kidney is rare and endemic in only certain parts of the world, the recent development of air travel, particularly for holidaymakers to countries such as Portugal where the disease is endemic, may result in the appearance of hydatid disease in countries previously uninfested. The incidence of renal hydatid disease in our series (0.028% of 28,332 urological patients) was surprisingly low when the endemic nature of the disease in Portugal is considered in relation to the low socio-economic status of the population in most rural areas.

From the clinical aspect, a hydatid cyst of the kidney may be totally asymptomatic (Sanjurjo, 1970). When symptoms occur it is usually a dull ache in the loin and renal colic only accompanies passage of hydatid material to the bladder. Urinary infection, sudden changes in general health or involvement of other organs may occur. Hypertension may also be associated with renal hydatid cysts (Truc and Grasset, 1962; Balesteros de Frutos, 1971; Bouvet *et al.*, 1972; Steg, 1975) and we observed this in one of our patients who became normotensive after nephrectomy.

Of the laboratory investigations, eosinophilia is useful as this is elevated in the presence of a cyst, but it may disappear whenever a cyst becomes infected. The Casoni intradermal test was not a valuable investigation in our series but this may have been due to the poor quality of the fluid used. Usually this test is positive in 75 to 95% of cases (Bradstreet, 1969; Sanjurjo, 1970; Gentilini and Pinon, 1972) but it is important to realise that false positive results have been noted in as many as 9 to 18% of cases with this test (Coudert, 1969, 1970; Sanjurjo, 1970). The Weinberg test (complement fixation test) has been reported to be less reliable than the Casoni test (Sanjurjo, 1970; Jimenez *et al.*, 1975) and was negative in all of our patients. When the complement fixation test is positive it remains so provided there is a living cyst in the body and it becomes negative only on complete surgical excision or death of the cyst. Unfortunately, the Casoni test may remain falsely positive for several years after successful excision of a hydatid cyst (Dew, 1928; Kellaway and Fairley, 1932; Magath, 1941, 1953; Katz and Pan, 1958) and it would appear therefore that the complement fixation test would be the most helpful indicator of the existence of the parasite and could be particularly useful in determining those patients in whom residual parasitic tissue is present and those in whom it recurs after treatment.

When severe infection of a cyst occurs or a patient is too ill to withstand a major operation, it should be marsupialised, but sometimes it is safe merely to drain it pending further surgical treatment at a later date.

Nephrectomy may be the only form of treatment available sometimes, and formalinisation of a cyst on such occasions is not needed unless there is a danger that it will rupture during the operation. When partial nephrectomy is possible, injection of a 2% solution of formalin into the cyst should always be done. Our technique is first to aspirate the contents of the cyst through a large trocar and then inject an equal volume of formalin into it, leaving this undisturbed for 10 min; it is important to protect all adjacent areas from spillage of hydatid material by moist gauze packs. It is not possible to find a plane of cleavage between the adventitia of the cyst and normal kidney tissue in patients in whom conservative surgical treatment is undertaken because the adventitia of the cyst consists of modified renal parenchyma. Therefore, either the adventitia can be removed by sharp dissection or the adventitia can be left in place after removal of the hydatid contents of the cyst. This latter technique has been advised by Goinard *et al.* (1960) but it is important that, if this is done, loculation of the cyst within the remaining adventitia should be identified and removed, and any adventitial wall left after complete removal of the parasite should be swabbed with gauze soaked in formalin to eliminate any remaining infestation.

When partial nephrectomy is planned for removal of hydatid cysts that communicate with the pelvicaliceal system, the opening should always be closed and the urine drained from the kidney by a nephrostomy, pyelostomy or ureterostomy. In these cases, formalin instillation into the cyst before removal is contraindicated because this might damage the kidney and urinary tract if it enters the renal pelvis (Matos Ferreira *et al.*, 1969). On these occasions hypertonic saline injected into the cyst has been said to kill the parasite effectively, although we have no experience in its use. The wound should be drained in all cases.

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Evening Urinary Oxalate Excretion in Stone Formers

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Summary—Urine collections from stone formers and controls were made between 6 p.m. and midnight and analysed for oxalate content. No difference in oxalate output was found between these groups. This makes it unlikely that hyperabsorption of oxalate from the intestine is a common cause of idiopathic calcium oxalate stones. The convenience of 6-h urine collections for detecting hypercalciuria is discussed.

Calcium oxalate stones are common in developed countries (Sutor *et al.*, 1974) and also in certain cases of gastrointestinal disease (Earnest and Graham, 1976). Recurrent stone formers have been reported to have increased 24-h total calcium and oxalate outputs compared with controls (Robertson *et al.*, 1971) and studies of the circadian oxalate output in non-stone formers suggest increased output in the evenings (Hargreave *et al.*, 1977).

It is possible that an intestinal abnormality of oxalate absorption may account for some cases of calcium oxalate lithiasis and this could result in increased evening urinary oxalate output.

This study was undertaken to see if differences in oxalate output between stone formers and controls would be found using a 6-h evening collection.

Patients and Methods

Stone Formers

Thirty-eight male patients, average age 48, with radiological evidence of stones in either kidney or ureter were studied. Female patients were not included in this study, as the majority had a urinary infection associated with stone formation. Thirty of the male stone formers had evidence of recurrent stone formation and the remainder were new cases. Patients with either an infected urine, or receiving drug therapy affecting renal function, were excluded from this study. Also excluded were patients with overt gastrointestinal disease. Informed consent was obtained from all patients.

Controls

This group consisted of 35 male patients, average age 49, with no past history or radiological evidence of urinary tract stone. Patients included in this group were those with prostatic symptoms and those awaiting vasectomy or various forms of scrotal surgery. Patients with impaired renal function, infected urine, diagnosed gastrointestinal disease and those on regular drug therapy were excluded from the study. Informed consent was obtained from all patients in this group.

Urine collection was made from 6 p.m. until midnight by all patients. They were asked to maintain their normal diet and fluid intake, but to abstain from alcohol on the day of collection to prevent an abnormal diuresis. Written instructions were given to each patient, who was provided with a 500 ml sterile plastic container, previously used in the operating theatre for distilled water (Travenol), into which 5 ml of concentrated hydrochloric acid had been added as a preservative. Patients found the use of these containers and the timing of the collection more convenient than the regime for the standard 24-h collection.

The urine specimens were returned on the following morning and the volume was measured. The urine was not filtered and was refrigerated until analysis. Urine calcium, phosphate, uric acid, magnesium and creatinine concentrations were estimated by the hospital's biochemistry department. Oxalate estimation was performed using an enzymatic method (Hallson and Rose, 1974). The results were analysed statistically using Student's t test.

Results

The total oxalate output and concentration are

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Table 1 Total Oxalate Output and Concentration

	Stone formers		*Controls*		*P value*
	Mean ± SEM	*N*	*Mean ± SEM*	*N*	
Total oxalate μmol	137±13	38	154±12	35	NS
Oxalate concentration μmol/l	345±36	38	407±33	35	NS

Table 2 Urine Volume, Calcium, Phosphate, Magnesium, Uric Acid and Creatinine Concentrations

	Stone formers		*Controls*		*P value*
	Mean ± SEM	*N*	*Mean ± SEM*	*N*	
Volume ml	497±54	38	503±59	35	NS
Calcium mmol/l	5.6±0.6	31	3.3±0.4	33	<0.005
Phosphate mmol/l	19.1±3.4	28	23.3±3.3	32	NS
Magnesium mmol/l	2.2±0.3	30	1.9±0.2	32	NS
Uric acid mmol/l	1.3±0.2	29	1.6±0.2	32	NS
Creatinine mmol/l	9.7±0.8	30	9.4±0.9	33	NS

shown in Table 1 and no significant differences were found between these values. The urine volume and concentrations of calcium, phosphate, magnesium, uric acid and creatinine are shown in Table 2. The urine volume and creatinine concentrations were comparable between the 2 groups within narrow limits, which allows the other concentrations to be compared directly. The only statistically significant result was the difference between the concentrations of calcium in the 2 groups.

Discussion

Calcium oxalate stone formation appears to result from imbalance of urine saturation and urinary crystallisation (Robertson *et al.*, 1976).

There is evidence of abnormal oxalate absorption in a number of gastrointestinal disorders (Dowling *et al.*, 1971; Smith *et al.*, 1972; Earnest and Graham, 1976) and there is also evidence of increased urine oxalate output in recurrent stone formers (Robertson *et al.*, 1971). Our study was undertaken to see if we could detect stone formers with a latent gastrointestinal absorption abnormality causing transient episodes of hyperoxaluria. Previous work in normal subjects had suggested that this is most likely to appear in the evening (Hargreave *et al.*, 1977). However, in the present study there was no difference in oxalate output between the stone formers and controls. These observations would suggest that transient hyperoxaluria, due to a gastrointestinal abnormality, is unlikely to be a common cause of stone formation.

Six-hour urine collections may be a useful technique for detecting hypercalciuria but more studies are required to assess the value of this technique.

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Cutaneous Ureterostomy, the Preferred Diversion of the Solitary Functioning Kidney

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Summary—Ten cases of cutaneous ureterostomy are presented. The results illustrate that the fear of stenosis and slough in transplanting even a normal calibre ureter to skin is generally not warranted. The diversion of a solitary kidney to an interposed ileal segment is to be discouraged since it prolongs operation time and increases morbidity.

In 2 patients with stenosis of the stoma a revision involving the then-dilated ureter was easily performed.

Cutaneous ureterostomy seems to be the best and simplest method of diverting the urine to skin when adequate lengths of ureter and an accessible stoma site are available. Though first suggested in 1856 by Gignon, it was not until 43 years later that LeDentu performed the first deliberate cutaneous ureterostomy. By 1925 it was often used as a method of diversion (100 of 181 cases after total cystectomy by Papin), but has recently been relatively little used (Abeshouse, 1958). Because of advances in chemotherapy and radiotherapy, there are more patients in whom local pelvic malignancy has led to a silent loss of function of one kidney and contralateral hydroureter. When the patient's quality of life seems such that diversion is indicated, cutaneous ureterostomy is an eminently suitable and appropriate method of combating incipient azotaemia. An analysis of our experience with this type of diversion suggests that the fear of complications of stenosis, ureteric slough and abscess are exaggerated and, indeed, this operation can yield the best chance of tubeless, relatively carefree diversion. In 1962 Lloyd *et al.* presented 21 cases with fairly good results in which they performed a high cutaneous ureterostomy in order better to preserve the blood supply to the proximal end, and they fashioned a method of producing skin flaps for direct anastomosis to the spatulated ureter. In a recent personal communication Lloyd noted that in the 15 years since his report he was still enthusiastically in favour of cutaneous ureterostomy in selected cases.

Coetzee, however, in his Urological Surgeons' Prize Essay in 1966, stated that: "If the operation of cutaneous ureterostomy is limited to patients in whom the ureter is dilated, a satisfactory single stoma will be possible in every case. The operation should probably be done only in such cases." Lapides (1962) stated: "We are entirely in accord with the conclusion that transplantation of normal ureters to skin is precarious, regardless of the technique used, and we do not perform cutaneous ureterostomies in patients with normal ureters." McDonald (1968) stated that an undilated ureter constituted a contraindication to cutaneous ureterostomy and that: "It is far better to do a ureteroileostomy." It is this limitation that we feel should now be reassessed. Young and Aleida (1966) noted that flank ureterostomy proved to be a satisfactory method of unilateral diversion in all 11 patients in their group. Wagner and Kollias (1975) reported 74 cases of cutaneous ureterostomy with good results.

Methods

After the stomal site is marked (usually slightly anterior to the anterior axillary line and slightly inferior to the midpoint between the iliac crest and the twelfth rib), the ureter is approached in its middle third through an extraperitoneal flank incision. The ureter can be mobilised enough to bring it to the skin, but care should be taken to minimise denuding this structure and, where possible, blood supplies should be preserved. After transection, the ureteric course should be without angulation and occasionally a large, more direct tunnel may easily be fashioned through the retro-

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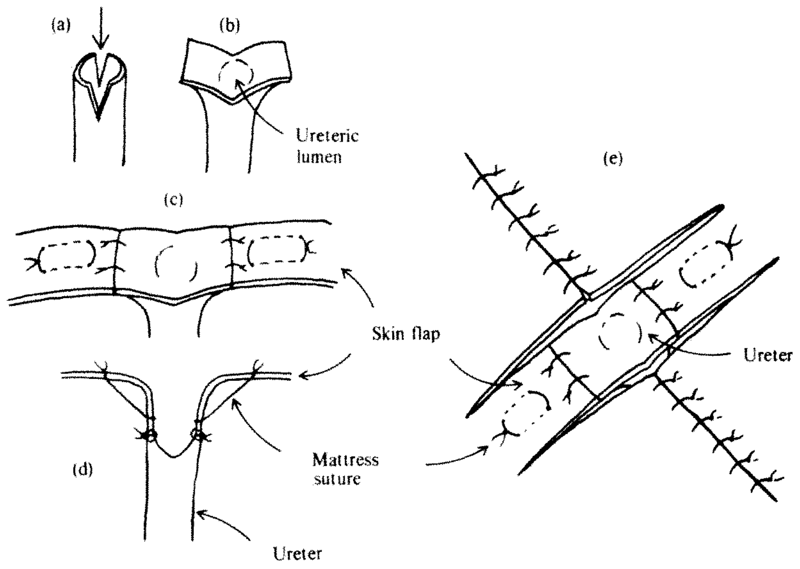

After Frederick A. Lloyd, M.D.

Fig. 1 Technique of stoma construction.

peritoneum and perinephric fat. Gerota's fascia may have to be incised if it is thick and impinging on the ureter. A single suture placed longitudinally through the fascia of the ureter to the muscle fascia may help to take tension off the skin anastomosis. Though we prefer the H-type of skin flap described by Lloyd *et al.* (1962) (Fig. 1), any type of carefully fashioned stoma will probably do well provided there is no tension and it is carefully approximated (Obrant, 1957).

Fine sutures of 4/0 are used for this anastomosis and an 8 or 10 FG catheter or paediatric feeding tube can be used for drainage for 5 to 7 days, after which a collection device is applied. A large catheter may compress the ureteric wall and interfere with blood flow to the stoma.

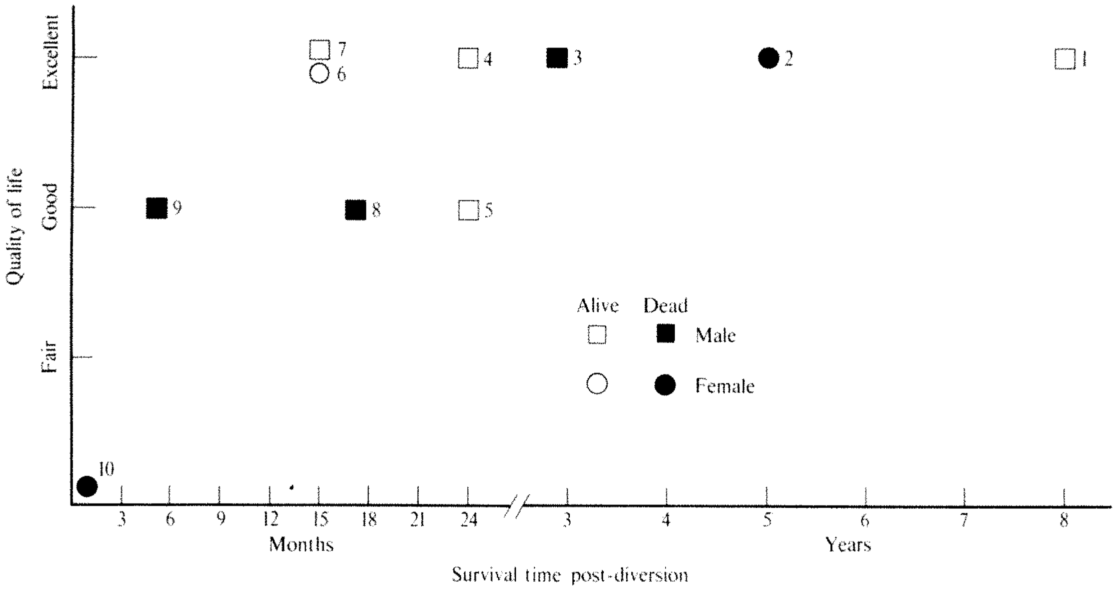

Fig. 2 Results of ureterocutaneous urinary diversions.

Table Profile of 10 Patients with Cutaneous Ureterostomy

Case		*Age*	*Primary disease*	*Post-operative*	*Alive*
1. M.I.	♂	59	Carcinoma bladder and ureter	8 years	√
2. M.C.	♀	49	Carcinoma bowel	5 years	
3. C.Mc.	♂	78	Carcinoma bladder	2 years, 10 months	
4. F.R.	♂	55	Carcinoma ureter and bladder	2 years	√
5. G.T.	♂	74	Contracted bladder	2 years	√
6. V.W.	♀	56	Carcinoma bladder	15 months	√
7. A.I.	♂	81	Carcinoma prostate	15 months	√
8. H.F.	♂	61	Carcinoma prostate	17 months	
9. A.N.	♂	78	Carcinoma bladder	5 months	
10. S.M.L.	♀	77	Carcinoma bladder	3 weeks	

Results

Cases reported and the results to date are summarised in the table and Figure 2.

Our one post-operative death (patient no. 10) was a 77-year-old who, following a transurethral resection of a large bladder tumour, a subsequent right nephroureterectomy for ureteric tumour and left cutaneous haemorrhage due to recurrent bladder transitional cell carcinoma, had a fatal myocardial infarction 3 weeks following cutaneous ureterostomy. A nephrostomy was done just prior to her death because of a periureteric abscess and distal ureteric necrosis. She had received 6200 rads of Cobalt 60, which devitalised her distal ureter.

Of the remaining cases, all have enjoyed excellent palliation from their cutaneous ureterostomy and, except for patient no. 5 (a 77-year-old with chronic inflammation and contralateral and vesical stone disease), all are, or were, tube-free with undilated upper tracts. Our second-longest survivor (patient no. 2) enjoyed a good quality of life and worked until one month prior to her death despite an added colostomy. Figure 3 illustrates the ingenuity of patient no. 1 (a 58-year-old with cancer of the bladder and a 5-year functioning stoma), who devised a hard rubber rod gently to obstruct the urine flow from the ostium prior to application of adhesives. He required a revision

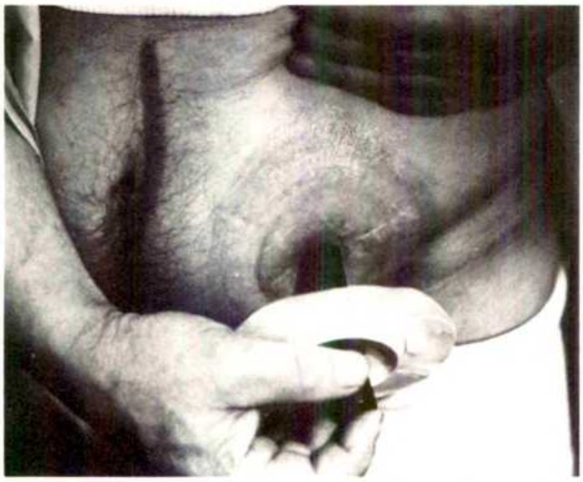

Fig. 3 Method of keeping area dry prior to application of adhesives. (Vaginal tampons may be used.). Patient no. 1.

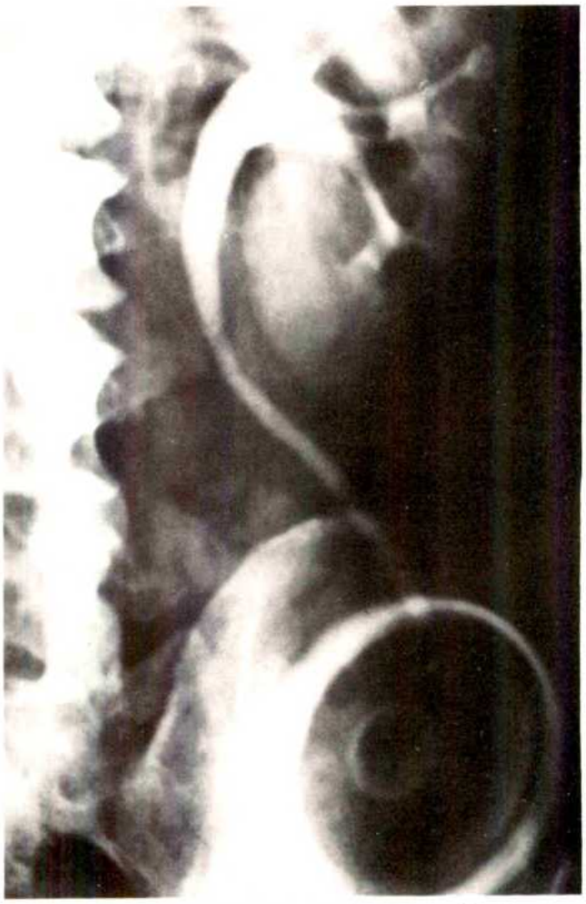

Fig. 4 Pyelogram 3 years after diversion and subsequent revision, showing excellent result. Patient no. 1.

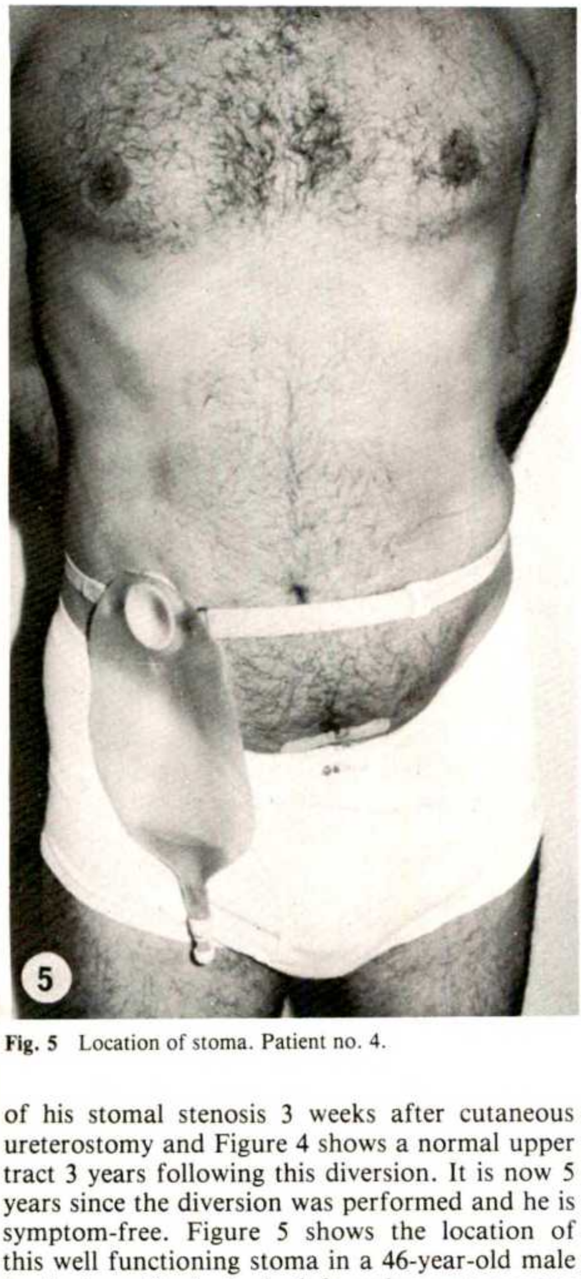

Fig. 5 Location of stoma. Patient no. 4.

of his stomal stenosis 3 weeks after cutaneous ureterostomy and Figure 4 shows a normal upper tract 3 years following this diversion. It is now 5 years since the diversion was performed and he is symptom-free. Figure 5 shows the location of this well functioning stoma in a 46-year-old male (patient no. 4) who had a left nephroureterectomy and a subsequent cystectomy, prostatectomy and urethrectomy for recurrent urothelial carcinoma. Figure 6 shows his excellent, delicate stoma. Most of these stomas appeared as a transverse slit.

Discussion

An analysis of our 10 cases suggests that when diversion of a solitary kidney is undertaken, cutaneous ureterostomy seems the method of choice. Except when contraindicated, *i.e.* short ureter, ectopic kidney, gross obesity, etc., this simple diversion should be considered. Seven normal calibre ureters were transplanted to the skin and 2 of them developed stenosis. These required later, simple revisions. *Vis-à-vis* uretero-ileocutaneous ureterostomy, one need only consider the added stress of entering the peritoneum, violating the bowel, constructing the ureteroileal as well as ileocutaneous junctions (with their inherent risk), to decide in favour of this much less stressful procedure. All but one of our patients are, or were, tube-free; one failed and required nephrostomy. The primary disease was cancer of the bladder in 6, of the prostate in 2, of the bowel in one, and one had a contracted bladder. The period of survival ranged to 8 years, and 5 of these 10 patients are alive. All but 2 of the ostia were created using an H-type skin flap. If basic principles of preservation of blood supply and avoidance of angulation and tension are respected, one can expect the transplant of a normal calibre ureter to skin to succeed.

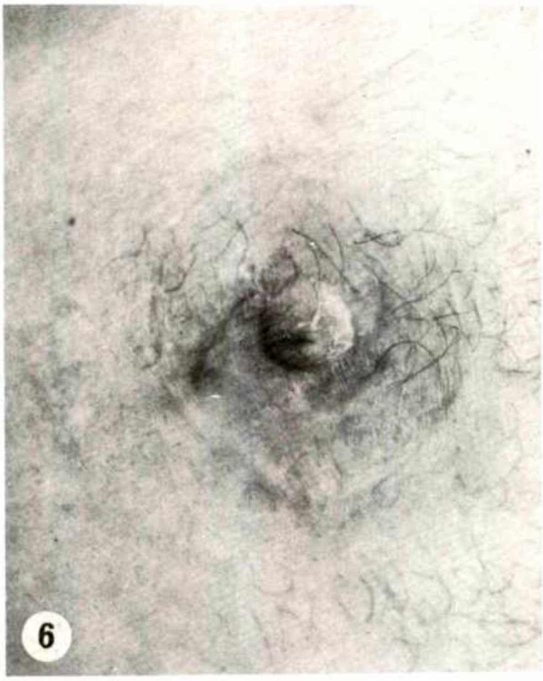

Fig. 6 Appearance of stoma. Patient no. 4.

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Vesicoureteric Reflux following Endoscopic Extraction of Lower Ureteric Calculi

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Summary—Twenty-three patients subjected to endoscopic ureteric meatotomy or Dormia extraction were examined for vesicoureteric reflux. Reflux into the lower third of the ureter was found in 2 asymptomatic patients.

The risks of reflux from endoscopic stone removal seem to be minimal.

Complications resulting from the extraction of a lower ureteric stone with the Dormia basket include avulsion of the ureter (Hodge, 1973) and ureteric perforation (Mahon and Waters, 1973). Often, following this procedure, there is iliac fossa pain, tenderness and haematuria, and the basket sometimes contains not only the ureteric stone but also small amounts of tissue presumably derived from the ureteric wall. This suggests that the procedure may well inflict enough damage on the ureteric orifice to allow vesicoureteric reflux to occur. Vesicoureteric reflux is a well recognised complication of endoscopic ureteric meatotomy whether this is performed for removal of a lower ureteric stone or for ureterocele (Roper and Smith, 1965; Roberts and Roylance, 1967). Such reflux would be a contributory factor to the development of urinary infection in stone patients and may help to produce further lithiasis and renal damage. This study was intended to ascertain whether endoscopic extraction of ureteral calculi carries a significant risk of long-term reflux, or whether the risks are largely theoretical.

Patients and Methods

Twenty-three patients who had previously had successful endoscopic extraction of a lower ureteric stone attended for follow-up assessment. Of these 23, 17 had had a stone removed by Dormia extraction, 5 by endoscopic ureteric meatotomy and one by both Dormia extraction and ureteric meatotomy at different times. The time interval between stone extraction and follow-up varied between 18 months and 11 years with a mean follow-up of 79 months for those patients who had had Dormia extractions and 58 months for those who had had a ureteric meatotomy. In all cases the stone had been extracted at the time of the endoscopy and in those cases having Dormia extractions the stone was removed within the basket. The only post-operative complication encountered was some iliac fossa pain. The presence or absence of urinary symptoms was ascertained in all patients and microscopy and culture of a catheter specimen of urine was performed. Each patient had a micturating cystogram, the bladder being filled with contrast until discomfort was felt and then screened during micturition, males standing and females sitting.

Results (Table)

All of the patients were asymptomatic except for one woman with symptoms of recurrent cystitis and 2 women with minimal loin pain, both known to have small stones in the kidney on that side. Reflux in the 2 patients in whom it occurred did not extend beyond the lower third of the ureter and both of these patients were asymptomatic. No patient had a significant pyuria or a positive urinary culture.

Table

	No. with reflux	*No. with pyuria or infected urine*
Dormia (17)	1	0
Meatotomy (5)	0	0
Both procedures (1)	1	0

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Discussion

It has not been possible to demonstrate significant reflux following endoscopic extraction of ureteric calculi. It would seem that despite the well documented short-term hazards of Dormia extraction, long-term damage to the valvular mechanism at the vesicoureteric junction is unlikely to occur. Whilst relatively few meatotomies have been performed for stone, none has produced reflux and this would seem to be a relatively safe procedure provided that the incision is limited to the minimal amount of cutting required to release the stone. Jacobsson and Sundin (1963) found that 4 out of 20 patients refluxed following ureteric meatotomy for stone but 3 of them had had more than one incision into the ureteric orifice. Failure to demonstrate reflux in this series may be because the procedure has been used only for stones seen to be protruding through the ureteric orifice and the length of the incision has been the minimum to release the stone. McAdam and James (1967) demonstrated reflux in 9 out of 11 patients following ureteric meatotomy but only one patient showed minor pyelographic deterioration, suggesting that reflux, should it occur, only occasionally produces renal damage. Dormia extraction, despite all its other hazards, seems to have only a slight risk of producing reflux

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A Comparison between Propantheline and Imipramine on Bladder and Salivary Gland Function

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Summary—The effects of propantheline and imipramine on detrusor function and salivary gland secretion were studied in the dog. Both drugs caused a decrease in the rise of intravesical pressure following pelvic nerve stimulation in the anaesthetised dog.

Propantheline had a profound effect on the salivary gland, whereas imipramine had very little effect on the volume of saliva produced after electrical stimulation of the chorda tympani.

This suggests that the action of imipramine on the bladder is not anticholinergic. The significance for treatment of detrusor dysfunction is discussed.

The drug treatment of detrusor instability is often unsatisfactory as the dosage of drugs required to influence detrusor function is so high that the patient is unable to tolerate the drug because of its side effects. Anticholinergic drugs are widely used, *e.g.* propantheline bromide (Pro-banthine), but the side effects, especially the dry mouth caused by reduced salivary gland secretion, limit the maximum dosage which the patient can tolerate. Another popular treatment is with the tricyclic antidepressant drugs, *e.g.* imipramine hydrochloride (Tofranil) which have atropine-like side effects. It is not known whether the primary action of imipramine is on the lower urinary tract, as suggested by Gregory *et al.* (1974), or through alpha adrenergic stimulation (Kharma *et al.* 1975). The present series of experiments was designed to compare the action of propantheline and imipramine on detrusor function and on salivary gland secretion, which is completely blocked by anticholinergic drugs (Langley, 1878).

Materials and Methods

Fifteen adult female dogs were used whose weight varied between 14 and 23 kg. Anaesthesia was induced with intravenous pentobarbitone (Nembutal) and maintained with nitrous oxide and oxygen supplemented by further doses of pentobarbitone if required.

An intravenous cannula was placed in a femoral vein to allow the administration of drugs and an intra-arterial catheter was inserted into a femoral artery to monitor changes of blood pressure. The abdominal cavity was opened. One of the pelvic nerves was dissected from the surrounding tissue and divided (Creed and Tulloch, 1978). Its distal end was placed over paired platinum electrodes. A 5 FG ureteric catheter was passed through the urethra into the bladder to monitor changes in intravesical pressure. Bladder volumes varied between 50 and 120 ml but were constant throughout the experiment apart from a small increase in volume from the production of urine by the kidneys.

The skin overlying the mylohyoid was divided in the midline and extended 10 cm inferiorly from the symphysis menti. The mylohyoid was divided in the midline and one lingual nerve was identified and dissected proximal to the point where the chorda tympani runs to the submandibular gland (Creed and Wilson, 1969). The nerve was divided and its distal end placed over paired platinum electrodes. The submandibular duct was cannulated where it passes deep to the lingual nerve. The cannula was directed so that the saliva from its distal end dropped through a photoelectric counter and the number of drops was recorded on a Grass polygraph (7C).

At the beginning of each experiment the voltage required to produce a maximum increase of bladder pressure and salivary flow was ascertained and just supramaximal voltage was chosen. The

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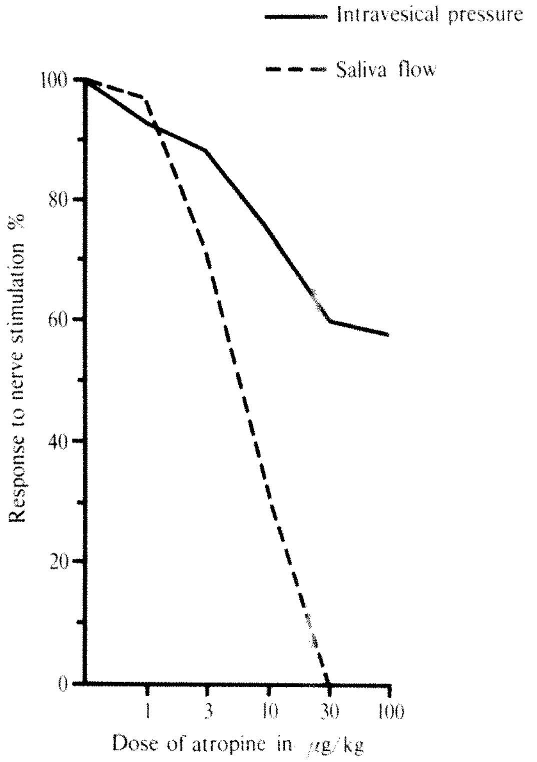

Fig. 1 Effect in 2 experiments of atropine on saliva flow and intravesical pressure produced by stimulation of chorda tympani and pelvic nerve respectively. The responses are expressed as a percentage of control values recorded prior to injection of atropine. The nerves were stimulated supramaximally at 10 Hz for 10 s.

pelvic nerves and lingual nerves were stimulated for 10 s at 2 min intervals with trains of pulses at 10 Hz from a Grass stimulator (SD9). This current stimulated only the pelvic nerves and did not cause contraction of adjacent smooth and striated muscle. Several base line readings were taken of the rise in bladder pressure and the number of drops of saliva which were produced in the 60 s from the start of electrical stimulation. In the first series of experiments, atropine was given intravenously in increasing doses ranging from 1 to 100 μg/kg. In the second series propantheline was used in doses of 1 to 300 μg/kg. In the third series, imipramine was given in doses between 1 μg and 3 mg/kg.

Results

The maximum rise of intravesical pressure with electrical stimulation varied between 5 and 26 mmHg. In the absence of nerve stimulation of the chorda tympani there was no saliva flow, but with stimulation the number of drops of saliva produced in one minute ranged from a minimum of 8 to a maximum of 48 drops. Increasing doses of atropine, propantheline and imipramine reduced the rise of intravesical pressure and the number of drops of saliva produced with electrical stimulation.

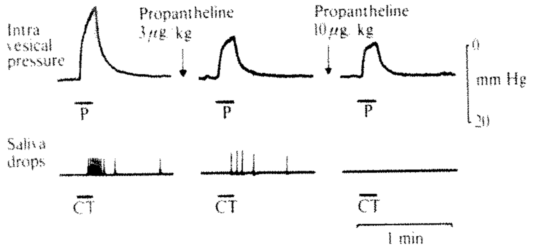

Fig. 2 Effect of 2 doses of propantheline on intravesical pressure with pelvic nerve stimulation (P) and drops of saliva with chorda tympani stimulation (CT).

Atropine totally abolished salivary gland secretion at a dose of 30 μg/kg but the rise of intravesical pressure was reduced by only 40% at the same dosage. Increasing doses of atropine produced no further reduction in intravesical pressure response to electrical stimulation and further confirmed the observation of atropine resistance of the bladder (Fig. 1).

Propantheline bromide almost completely blocked salivary gland secretion at 10 μg/kg but produced only a 25% reduction of the intravesical pressure to pelvic nerve stimulation (Fig. 2). With higher doses of propantheline there was a further sharp reduction in the response to pelvic nerve stimulation (Fig. 3). This reduction was probably due to the ganglion blocking properties of propantheline at very high doses.

The responses to imipramine were different. At low doses—up to 100 μg/kg—there was very little change in salivary production, but already a 15% fall in intravesical pressure response (Fig. 4). Thereafter, with increasing doses of imipramine there was a marked reduction in the intravesical pressure response to pelvic nerve stimulation with very little further fall in salivary gland secretion (Fig. 5). In the doses of 3 mg/kg and higher, cardiovascular side effects were noted with the production of arrhythmias and transient falls in blood pressure.

Discussion

The present experiments confirm that both pro-

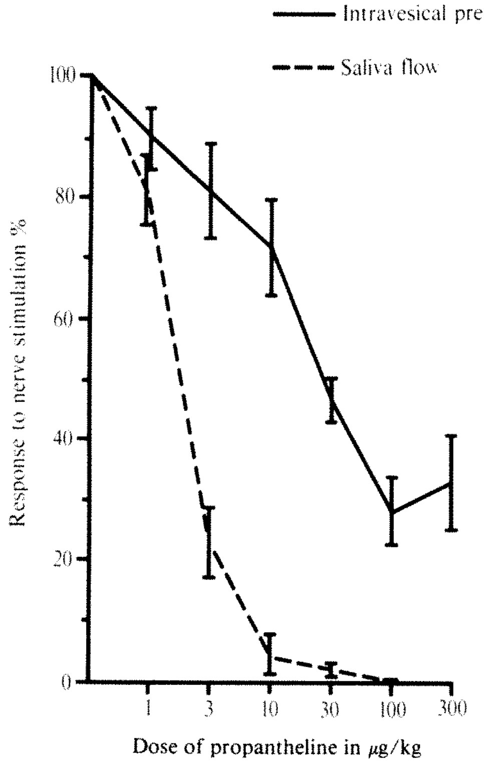

Fig. 3 Effects of propantheline on saliva flow and intravesical pressure, induced by nerve stimulation. Vertical bars represent Standard Error of the Mean of 6 experiments.

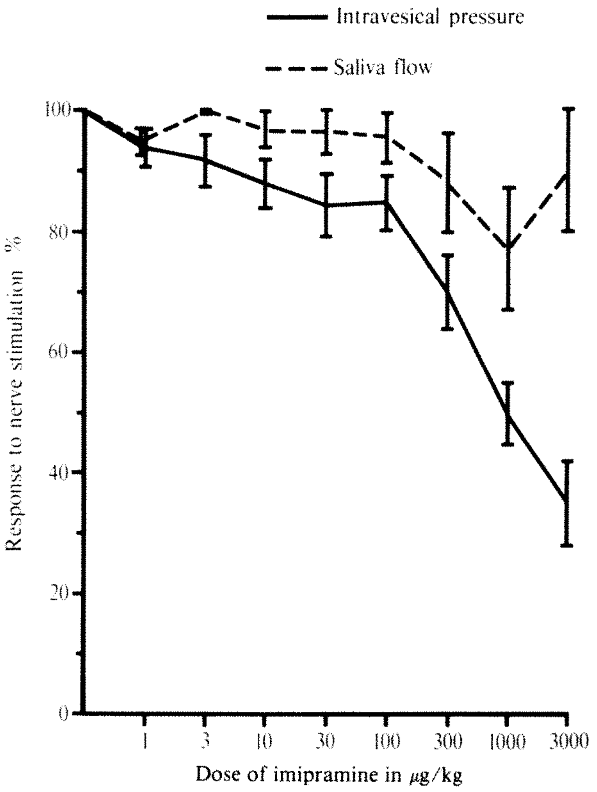

Fig. 4 Effect of imipramine on saliva flow and intravesical pressure, recorded from 7 experiments.

pantheline and imipramine reduce the pressure responses of the bladder to pelvic nerve stimulation (Gregory *et al.*, 1974). However, the inhibition to imipramine was greater at therapeutic doses than the inhibition to propantheline. On the other hand, propantheline completely abolished submandibular saliva flow to stimulation of the chorda tympani, whereas imipramine had very little effect.

The precise mode of action of imipramine is not known and, in common with other tricyclic antidepressant drugs, it has central and peripheral actions (Goodman and Gilman, 1975). The present results indicate that a direct action on bladder musculature or its innervation must occur. This could be due to the postulated anticholinergic action of imipramine, resulting in tachycardia, constipation, dry mouth, etc., or its ability to block the re-uptake of biogenic amines such as noradrenaline and 5-hydroxytryptamine, so that local concentrations of these transmitters increase.

The chorda tympani, the parasympathetic innervation to the submandibular gland, contains only cholinergic fibres and it has long been known that the secretory responses to its stimulation are completely blocked by relatively low doses of atropine (Langley, 1878). Propantheline, another anticholinergic drug, also completely abolished secretion. Imipramine, however, had only a slight inhibitory action. This suggests that it has very little cholinergic blocking action and the dry mouth is more likely to be due to central inhibition of the salivary reflex.

The contractile response of the bladder to pelvic nerve stimulation is only partially blocked by

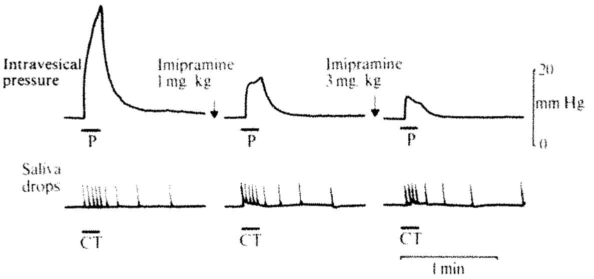

Fig. 5 Effect of 2 doses of imipramine on intravesical pressure with pelvic nerve stimulation (P) and drops of saliva produced with chorda tympani stimulation (CT).

atropine (Ursillo and Clark, 1956) or propantheline. This suggests that some of the excitatory fibres are not cholinergic and these may be the ones inhibited by imipramine. Close arterial injection of a number of drugs, including 5-hydroxytryptamine, adenosine triphosphate (ATP) and histamine, produced an increase in intravesical pressure in the dog (Kharma *et al.*, 1975; Creed and Tulloch, 1978) and could possibly be transmitters at the lower urinary tract. Alternatively, there is evidence that the action of noradrenaline inhibits the contractile responses to pelvic nerve stimulation (Hindmarsh *et al.*, 1977; Creed, 1979). If the pelvic nerve contains adrenergic fibres, imipramine could increase extracellular concentrations of noradrenaline by blocking uptake. Experiments are now in progress to elucidate this further.

The present experiments on the dog, therefore, do not support the conclusion that imipramine influences detrusor instability by an anticholinergic action. This supports the results of Diokno *et al.* (1972), who believe the improvement in enuresis after treatment with imipramine occurs only in patients whose enuresis is functional, whereas Cole and Fried (1972) have noted encouraging results in patients with neurogenic bladders after treatment with imipramine. Propantheline is useful in the control of symptoms of detrusor instability (Tulloch, 1978) but Turner Warwick (1975) has pointed out that many patients who are subjectively improved on drug therapy show no objective improvement on urodynamic testing.

This experimental work shows that imipramine causes a greater reduction in the bladder pressure rise with pelvic nerve stimulation than propantheline in doses which cause less than 50% reduction of salivary gland secretion. This suggests that imipramine is the more promising drug in the treatment of detrusor dysfunction, but possibly better clinical results may be obtained if both propantheline and imipramine were used simultaneously as the pharmacological action of each drug seems different.

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Giggle Incontinence (Enuresis Risoria). A Study and an Aetiological Hypothesis

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Summary—Questionnaires answered by 99 student nurses concerning bladder responses to laughter showed that roughly 25% had experienced such reactions at some time in their lives and about 10% could still register such phenomena at the end of their second decade. Giggle incontinence is not a condition confined to an "all or nothing" response of complete micturition. The evidence seems to indicate that the condition is due to some inborn and quite ordinary trigger mechanism exposed by physiological variations in sensitivity or specific control.

Giggle incontinence is the occurrence of involuntary uncontrollable voiding induced by laughter. The situation differs essentially from the common phenomenon of stress incontinence during laughter. Giggle incontinence is of the urge type, the laughter (or giggle) suddenly giving rise to acute urgency, almost immediately followed by micturition which cannot be stopped until the bladder is empty. Williams (1958, 1968) has briefly outlined the characteristics and Cooper (1973) reviewed the condition. It is often familial and occurs in both sexes, most commonly in the female. Typically it starts at about the age of 5 to 7 years, while older patients often claim they "always" had it. It is most common during school age and tends to improve or disappear with increasing age, but may persist into adult life. The tendency towards spontaneous cure obscures results of therapeutic efforts, but no convincing treatment has been reported.

The term "giggle micturition" has been suggested (MacKeith, 1964) to emphasise its distinction from stress incontinence in the same circumstances. Presumption of a special quality of the laughter as responsible for the phenomenon gave rise to the term "ambivalent laughter micturition" (Millard, 1965, 1966). De Jonge (1975) introduced the term "enuresis risoria" to classify the micturition as normal apart from its involuntary occurrence and relationship to laughter. While MacKeith (1959, 1964) and Millard (1965, 1966) suggested that there were psychological aspects in the aetiology, most authors consider giggle incontinence to be a specific disturbance caused by some unknown disorder in the central nervous system. The results of neurological examination, including electroencephalography, are normal, as are the urological findings; even detailed urodynamic investigations to disclose signs of bladder instability are negative in these patients (Turner Warwick, 1973).

Reports of giggle incontinence are scarce, but years of interest in the subject have given the author a growing impression that it is quite a common occurrence in girls and women, and that there are varying degrees of the phenomenon. Cooper (1973) also claimed that it occurred more frequently than the medical profession realises, as probably very few of the sufferers see a doctor about it. Some people are ashamed or too shy to mention the problem. By instinct they usually discover that the only way of managing the trouble is to reduce indulgence in laughter. The coining of a standard phrase like "I laughed so much I wet my pants", which finds parallel in most languages, also suggests a common experience. In the equally common expression "I laughed so much I nearly wet myself", the word "nearly" suggesting that even urgency alone may be a response to laughter, representing a precursor of giggle incontinence which can be checked. To investigate the validity of these assumptions a study of the incidence and types of response to laughter was undertaken.

Materials and Methods

Questionnaires were distributed to 120 student nurses at the hospital's school of nursing and were returned by 100. One was excluded because of

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Table Reactions to Laughter Reported by 24 Student Nurses Related to Age*

Case no.	*Pre-school age*	*Primary school (7-11 years)*	*Junior school (12-15 years)*	*16-18 years*	*The past year*	*Comment*
81	complete † (?)	complete (?)	urgency (?)	0	0	male
19	complete (often)	complete (often)	complete (once)	leakage ‡ (?)	leakage (2-3x/month)	
9	leakage (?)	complete (1-4x/year)	leakage (1x/year)	leakage (1x/year)	0	
12	complete (1-2x/year)	complete (1-2x/year)	leakage (1-2x/year)	leakage (1-2x/year)	leakage (1-2x/year)	
23	complete (once)	leakage (1-4x/year)	0	0	0	
58	0	complete (once)	0	0	0	
46	?	?	complete (once)	0	urgency	
27	0	complete (once)	0	0	0	
10	leakage (1-4x/year)	leakage 1-4x/year)	leakage (1-4x/year)	leakage (1-4x/year)	leakage (1-4x/year)	Had to sit on a special tray whenever she saw a funny film on TV!
97	leakage (?)	leakage (?)	0	0	0	
7	?	?	leakage (1-4x/year)	leakage (1-4x/year)	leakage (1-4x/year)	Mother and grandmother have the same troubles sometimes with complete micturition
56	?	?	leakage (2-3x/year)	leakage (2-3x/year)	urgency (5-6x/year)	
50	?	?	leakage (2-3x/month)	leakage (2-3x/month)	leakage (1x/month)	
31	?	leakage (1-2x/year)	leakage (1-2x/year)	0	0	
11	?	?	leakage (?)	0	0	
6	0	0	0	leakage (1-4x/year)	0	
68					leakage (2-3x/month)	Incomplete answer. Anonymous.
52			urgency (1-4x/year)			Incomplete answer. Anonymous.
32	0	0	0	urgency (2-4x/year)	0	Only during a skiing holiday 9 months ago (—15°C) but several times every day
87	0	0	0	0	urgency (→)	
33 62 48 59	stated urgency caused by laughter but gave no details. Anonymous					

* Upper line: the most pronounced reaction to laughter; brackets in lower line: rough estimate of frequency of that reaction.
0 = no reaction to laughter.
? = does not remember.
† Complete = complete micturition.
‡ Leakage = incomplete micturition.
For further details see text.

known bladder pathology, leaving 99 students for the study (7 male, 92 female) aged 19 to 26 years (mean 21.7 years). The questionnaires enquired about personal experiences of a sudden acute urge to void being provoked by laughter and whether such urgency sometimes resulted in complete micturition or in some lesser wetting of the clothes (leakage). Relationship to age, a rough estimate of the frequency of episodes and some supplementary questions on ordinary bladder control were included. The fundamental difference between the situation in question and stress incontinence during laughter was exhaustively explained and emphasised in the questionnaire, which was to be returned in a closed envelope, signed if the person agreed to a possible subsequent interview, anonymous if not. Statements of positive experience with incomplete details necessitated personal contact with 10 students, but this could not be carried out in 6 similar, but anonymous, cases.

Results

Of the 99 students 75 had never had such an experience. Twenty-four students (1 male, 23 female) reported reactions to laughter (Table), 8 with complete micturition (none, however, since the age of junior school and 3 only once), 9 with urgency and partial micturition (leakage), 7 with urgency alone.

At the time of investigation 10 from this group with positive experiences no longer had such reactions, 9 still experienced a response of urgency which 6 of them only partially managed to control, as evidenced by some leakage; 5 inadequate answers left doubt concerning the present situation.

The table registers only the most extreme reaction (with corresponding frequency). However, less pronounced reactions might occur during that same period. For instance, during the years of junior school case 46 had urgency from laughter at intervals of months but only complete micturition once, and never leakage. In case 56 only half of the episodes of urgency caused leakage at the age of 12 to 15 years and in case 50 the present situation is of urgency 2 or 3 times a month, causing leakage only about once a month.

Sudden urgency could not be induced by other stimuli in 11 cases; cold could act as a stimulus in 7 and fear or nervous strain in 4. In 2 a slight sensation of bladder fullness could increase to acute urgency at the moment the door of their own toilet came into sight. All of the students with reactions to laughter had otherwise obtained full control of bladder function day and night at the usual age, except case 81, who did not achieve this until he was 8 years old. The length of the usual interval between first bladder sensation and urgency (apart from situations of laughter) was taken as an indication of general bladder control; of those with persistent reactions of leakage at the time of investigation, this interval was classified as long (½-1 h) in 2, short (about 15 min) in 3, whereas 1 would look for a toilet at the first warning. Of those with urgency as the only persisting reaction, all 3 stated that this interval was long. Among the 75 students who had never experienced reactions to laughter, 68 reported long intervals, 5 short and 2 would look for a toilet at once.

Discussion

The assumptions were confirmed. Although the details reported in the table are only rough estimates, the main features are clear and incontestable. It seems that roughly 25% of young women have had such experiences at some time and moderate degrees may still occur in roughly about 10% at the end of the first 2 decades of life.

The apparent normality of the sufferers combined with the age relationship, the common occurrence and a full range of varying degrees suggest that giggle incontinence may not constitute a qualitative disorder but represent only a quantitative deviation from normal control of a quite ordinary response to laughter. The study supplied little evidence of otherwise lowered bladder control. Apparently laughter or giggling constitutes a specific stimulus working by some trigger mechanism to activate the micturition reflex, the giggle incontinence representing only physiological variations in sensitivity or specific control.

It is easy to bring out the typical features of the condition on direct questioning about laughter relationship and details of the type of incontinence; adequately guided, all the cases from my clinical practice could distinguish urge incontinence from stress incontinence. Thus a detailed and careful interview is all that is necessary to establish the diagnosis. Giggle incontinence may, however, coexist with other types of incontinence which should then be explored and treated separately.

It is concluded that giggle incontinence is not a condition confined to an "all or nothing" response of complete micturition. It is a common occurrence, the degree varying in relation to age. This evidence, combined with the normal results of all urological and neurological examinations in such cases, does not support the hitherto predominant hypothesis of the aetiology as a specific disorder of the central nervous system, in the sense of some unphysiological process, but rather supports a hypothesis ascribing the condition to some inborn and quite ordinary trigger mechanism exposed by physiological variations in sensitivity or specific control.

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The Value of Kanamycin-Colistin Bladder Instillations in Reducing Bacteriuria during Intermittent Catheterisation of Patients with Acute Spinal Cord Injury

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Summary—Two groups of patients with acute spinal cord trauma had initial bladder management by standard non-touch techniques of intermittent catheterisation. Twenty-two patients (17 males and 5 females) had kanamycin-colistin solution instilled into the bladder at the end of each catheterisation, and 25 patients (21 males and 4 females) were not given these instillations.

The incidence of significant bacteriuria during intermittent catheterisation of both males and females receiving the instillations was only half the incidence of those not receiving the instillations. Also, a significantly higher proportion of males receiving the instillations did not have any episodes of significant bacteriuria compared with those not receiving the instillations, and the same trend was evident in the small number of female patients. It is recommended that patients should have kanamycin-colistin bladder instillations when they are being intermittently catheterised.

The incidence of episodes of significant bacteriuria during catheterisation of patients with acute spinal cord trauma can be reduced to a low level by using strict non-touch techniques of intermittent catheterisation and instilling kanamycin 150 mg plus colistin 30 mg in 25 ml of sterile water into the bladder at the end of each catheterisation (Pearman, 1971, 1977). The improved techniques of aseptic catheterisation and the use of kanamycin-colistin instillations were introduced simultaneously at the Perth Spinal Department on 1 February 1968. Consequently there had not been an opportunity to determine whether kanamycin-colistin instillations produced a significant reduction in the incidence of urinary tract infections below that which occurred when strict aseptic intermittent catheterisation was practised. When Harper and Matz (1975, 1976) showed that several antimicrobial solutions used for irrigating human bladders frequently caused erosive cystitis in the rat bladder, it became clinically important to determine whether or not kanamycin-colistin bladder instillations were of value in reducing urinary tract infections in spinal cord injured patients while they were being intermittently catheterised.

Patients and Methods

Two groups of patients were studied: those admitted during the period 1 February 1976 to 31 January 1977 (group A), and those admitted from 1 February 1977 to 31 January 1978 (group B). All catheterisations, in both groups, were carried out according to the standard non-touch techniques of intermittent catheterisation used in the Perth Spinal Department (Pearman and England, 1973). Patients in group A had kanamycin-colistin solution injected into the bladder at the end of each catheterisation; those in group B were not given the instillations. A specimen of urine was obtained for culture at every catheterisation and each episode of significant bacteriuria was treated by giving appropriate systemic chemotherapy for 7 days. The incidence of significant bacteriuria during the period of intermittent catheterisation in both groups of patients was compared.

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Table 1 Classification of Bladders

Bladder classification	*Male*		*Female*	
	A	B	A	B
Normal	5	4	1	2
Upper motor neurone				
Incomplete (tetraplegic)	2	–	–	–
(paraplegic)	2	–	–	–
Complete (tetraplegic)	5	14	1	–
(paraplegic)	3	2	3	1
Lower motor neurone				
Incomplete	–	1	–	–
Complete	–	–	–	1
Total	17	21	5	4

Twenty-five patients (19 males and 6 females) admitted to the Spinal Department with acute spinal cord trauma during the period 1 February 1976 to 31 January 1977 required catheterisation for more than 5 days. Two males died whilst on intermittent catheterisation, one from bronchopneumonia and the other from pulmonary embolism. A 14-year-old girl with fractured sacrum, pelvis and T.12 and L.1 vertebral bodies, who was incompletely paraplegic below L.3, was managed by means of an indwelling catheter for the first 19 days. The remaining 22 patients (17 males and 5 females) comprised group A (Table 1).

Twenty-eight patients (22 males and 6 females) admitted to the Spinal Department with acute spinal cord injury during the period 1 February 1977 to 31 January 1978 needed to be catheterised for more than 5 days. One male succumbed to bronchopneumonia; one female died from respiratory failure and cardiac arrest, and another female was admitted 23 days after injury with an indwelling catheter. The remaining 25 patients (21 males and 4 females) constituted group B (Table 1).

Both groups of patients consisted of males and females with acute spinal cord trauma and bladder involvement admitted consecutively to the Perth Spinal Department during the respective periods. No attempt was made to match the patients in group B with those in group A. Nevertheless, there were no significant differences in the 2 series in respect of the sex ratio or the mean ages of males; 77% of the patients in group A and 84% of those in group B were males. The mean age of the 17 males in group A was 30 years with a range of 16 to 59. The mean age of the 21 males in group B was 37 years with a range of 18 to 81. On 36 degrees of freedom t = 1.139 which is not significant. There was an insufficient number of females to enable a statistically significant comparison of the mean ages of female cases in each group to be made.

Urological surgery was performed on 5 male patients in group A. External urethral sphincterotomy was done on 3 tetraplegics and one paraplegic with complete upper motor neurone (UMN) bladders. One paraplegic with a complete UMN bladder required transurethral resection of the bladder neck in addition to division of the external urethral sphincter. Three tetraplegics with complete UMN bladders in group B also had external urethral sphincterotomy performed. All of these patients had indwelling catheters for 24 to 48 h post-operatively and one of them (the paraplegic with the combined procedure) developed a urinary tract infection during the post-operative period.

Classification of Bladders

The method used for classifying the type of neuropathic bladder dysfunction of these patients has been described previously (Pearman, 1976). The bladder classifications of the patients in this study are listed in Table 1. Six patients in group A (5 males and 1 female) and 6 patients in group B (4 males and 2 females) eventually regained normal bladder function, although several of them took more than 3 months to do so. The remaining 35 patients (12 males and 4 females in group A, and 17 males and 2 females in group B) had varying degrees of permanent bladder dysfunction due to spinal cord damage.

The strict bacteriological criteria for the diagnosis of significant bacteriuria, shown in Table 2, were adhered to throughout the investigation.

An episode of significant bacteriuria was usually represented by more than one positive culture being obtained. It referred to a series of consecutive positive cultures with the same species

Table 2 Criteria for the Diagnosis of Significant Bacteriuria

The bladder was considered to be infected if catheter specimens showed:

Colony count > 1000 per ml with same species of micro-organism in 3 consecutive specimens if catheters passed every 6 or 8 h, or in 2 consecutive specimens if catheterised every 12 h.

Colony count > 10,000 per ml in one specimen if catheter passed daily.

Table 3 Duration of Intermittent Catheterisation of Male Patients

Group	*Bladder classification*	*Period of intermittent catheterisation (days)*					
		9-30	31-60	61-90	91-120	121-150	151-180
A	Normal	3	1	1	-	-	-
	Incomplete UMN (tetraplegic)	-	2	-	-	-	-
	Incomplete UMN (paraplegic)	-	2	-	-	-	-
	Complete UMN (tetraplegic)	-	1	1	-	2	1
	Complete UMN (paraplegic)	-	1	1	1	-	-
	Total	3	7	3	1	2	1
B	Normal	1	3	-	-	-	-
	Complete UMN (tetraplegic)	-	2	5	3	1	3
	Complete UMN (paraplegic)	-	1	1	-	-	-
	Incomplete LMN	-	-	-	1	-	-
	Total	1	6	6	4	1	3

Up to 120 days = 31 (82%)

More than 120 days = 7 (18%)

of micro-organism being present for several days, until eliminated by an appropriate antimicrobial agent. Once an episode of significant bacteriuria had been eliminated by systemic chemotherapy, recurrence was regarded as a new episode, regardless of whether it was due to the same species or a different species of micro-organism. However, an exception was made in those instances where recurrence with the same species of micro-organism occurred within 7 days of ceasing the antibiotic, when it was considered to be a relapse of the original episode.

It was considered that intermittent catheterisation was being performed if a patient required catheterisation at least once every 24 h or at more frequent intervals. If catheterisation was performed on alternate days or at longer intervals it was considered that catheters were being passed for the purpose of checking the residual urine and not because the patient was still dependent on catheterisation for adequate bladder emptying.

Results

Duration of Intermittent Catheterisation and Number of Catheterisations Male Patients

Tables 3 and 4 show the details of intermittent catheterisation of male patients. Eight of the 9

Table 4 Number of Times Male Patients were Intermittently Catheterised

Group	*Bladder classification*	*Number of catheterisations*						
		11-50	51-100	101-200	201-300	301-400	401-500	501-600
A	Normal	3	1	1	-	-	-	-
	Incomplete UMN (tetraplegic)	-	1	1	-	-	-	-
	Incomplete UMN (paraplegic)	1	-	1	-	-	-	-
	Complete UMN (tetraplegic)	-	-	2	-	2	1	-
	Complete UMN (paraplegic)	-	1	1	-	1	-	-
	Total	4	3	6	-	3	1	-
B	Normal	1	3	-	-	-	-	-
	Complete UMN (tetraplegic)	1	-	6	2	3	-	2
	Complete UMN (paraplegic)	-	-	2	-	-	-	-
	Incomplete LMN	-	-	-	-	1	-	-
	Total	2	3	8	2	4	-	2

Up to 400 catheterisations = 35 (92%)

More than 400 catheterisations = 3 (8%)

Table 5 Duration of Intermittent Catheterisation of Female Patients

Group	*Bladder classification*	*Period of intermittent catheterisation (days)*				
		12-30	31-60	61-90	91-120	121-150
A	Normal	1	-	-	-	-
	Complete UMN (tetraplegic)	-	1	-	-	-
	Complete UMN (paraplegic)	-	-	1	1	1
	Total	1	1	1	1	1
B	Normal	2	-	-	-	-
	Complete UMN (paraplegic)	-	-	-	1	-
	Complete LMN	-	-	1	-	-
	Total	2	-	1	1	-

Up to 120 days = 8 (89%)

More than 120 days = 1 (11%)

males who regained normal bladder function became catheter-free within 60 days and had less than 101 catheterisations. The 4 males with incomplete upper motor neurone bladders became catheter-free within 60 days and had less than 201 catheterisations. In contrast, only 5 of the 24 patients with complete upper motor neurone bladders were able to dispense with the need of catheterisation within 60 days, and it took 120 days for 17 of them (71%) and up to 400 catheterisations for 21 of them (88%) to become catheter-free. The single male with an incomplete lower motor neurone bladder was intermittently catheterised for 109 days (337 catheterisations). Overall, 31 (82%) of the 38 males were catheterised for up to 120 days (Table 3) and 35 (92%) of them had up to 400 catheterisations each (Table 4).

Female Patients

The details of intermittent catheterisation of female patients are displayed in Tables 5 and 6. All of the 3 females who regained normal bladder function became catheter-free within 18 days and none of them required more than 43 catheterisations. In contrast, all but one of the 6 females with complete upper or lower motor neurone bladders were catheterised more than 100 times for periods of longer than 60 days. Overall, 8 (89%) of the 9 females were catheterised for up to 120 days (Table 5) and had up to 400 catheterisations each (Table 6).

Incidence of Significant Bacteriuria During Intermittent Catheterisation of Male Patients

Group A If the presence of established bacteriuria in one patient on admission is not in-

Table 6 Number of Times Female Patients were Intermittently Catheterised

Group	*Bladder classification*	*Number of catheterisations*					
		35-50	51-100	101-200	201-300	301-400	401-500
A	Normal	1	-	-	-	-	-
	Complete UMN (tetraplegic)	-	1	-	-	-	-
	Complete UMN (paraplegic)	-	-	1	1	-	1
	Total	1	1	1	1	-	1
B	Normal	2	-	-	-	-	-
	Complete UMN (paraplegic)	-	-	-	-	1	-
	Complete LMN	-	-	-	-	1	-
	Total	2	-	-	-	2	-

Up to 400 catheterisations = 8 (89%)

More than 400 catheterisations = 1 (11%)

Table 7 Mean Incidence of Significant Bacteriuria During Intermittent Catheterisation of Male Patients in Group A

Episodes of significant bacteriuria per patient	*Number of patients*	*Summation of episodes of significant bacteriuria*
0	9	0
1	1	1
2	4	8
3	1	3
4	2	8
Total	17	20

Total number of catheterisations = 2651

Mean incidence of significant bacteriuria = $\frac{20}{2651}$ = 1 per 133 catheterisations (0.75%)

Established bacteriuria present in one patient on admission was not included.

cluded, 9 of the 17 male patients did not have any episodes of significant bacteriuria during the period of intermittent catheterisation. One patient had one episode, 4 patients had 2, one patient had 3, and 2 patients each had 4 episodes, giving a total of 20 episodes of significant bacteriuria in the male patients of group A (Table 7).

A total of 2651 catheterisations was performed on the 17 males in group A. The average incidence of significant bacteriuria in these patients was one per 133 catheterisations, *i.e.* overall 0.75% of catheterisations resulted in an episode of significant bacteriuria in male patients of group A (Table 7).

Group B If the presence of established bacteriuria in one patient on admission is not included, 2 of the 21 male patients had no episodes of significant bacteriuria during the period of intermittent catheterisation. Five patients each had one episode, 3 patients had 2, 3 patients had 3, 4 patients had 4, 2 patients had 5, one patient had 8 and one patient had 10 episodes, giving a total of 64 episodes of significant bacteriuria in the male patients of group B (Table 8).

A total of 4460 catheterisations was performed on the 21 males in group B. The average incidence of significant bacteriuria in these patients was one per 70 catheterisations, *i.e.* overall 1.43% of catheterisations resulted in an episode of significant bacteriuria in male patients of group B (Table 8).

Table 8 Mean Incidence of Significant Bacteriuria During Intermittent Catheterisation of Male Patients in Group B

Episodes of significant bacteriuria per patient	*Number of patients*	*Summation of episodes of significant bacteriuria*
0	2	0
1	5	5
2	3	6
3	3	9
4	4	16
5	2	10
8	1	8
10	1	10
Total	21	64

Total number of catheterisations = 4460

Mean incidence of significant bacteriuria = $\frac{64}{4460}$ = 1 per 70 catheterisations (1.43%)

Established bacteriuria in one patient on admission was not included.

Incidence of Significant Bacteriuria During Intermittent Catheterisation of Female Patients

Group A Two of the 5 female patients did not have any episodes of bacteriuria during the period of intermittent catheterisation. One patient had one episode, another had 3 episodes and another patient had 7 episodes, resulting in a total of 11 episodes of significant bacteriuria in the female patients of group A (Table 9).

A total of 1025 catheterisations was carried out on the 5 females. The average incidence of significant bacteriuria in these patients was one per

Table 9 Mean Incidence of Significant Bacteriuria During Intermittent Catheterisation of Female Patients in Group A

Episodes of significant bacteriuria per patient	*Number of patients*	*Summation of episodes of significant bacteriuria*
0	2	0
1	1	1
3	1	3
7	1	7
Total	5	11

Total number of catheterisations = 1025

Mean incidence of significant bacteriuria = $\frac{11}{1025}$ = 1 per 93 catheterisations (1.07%)

Table 10 Mean Incidence of Significant Bacteriuria During Intermittent Catheterisation of Female Patients in Group B

Episodes of significant bacteriuria per patient	*Number of patients*	*Summation of episodes of significant bacteriuria*
1	2	2
6	1	6
10	1	10
Total	4	18

Total number of catheterisations = 727

Mean incidence of significant bacteriuria = $\frac{18}{727}$ = 1 per 40 catheterisations (2.48%)

Established bacteriuria present in one patient on admission was not included.

93 catheterisations, *i.e.* overall 1.07% of catheterisations resulted in an episode of significant bacteriuria in female patients of group A (Table 9).

Group B The presence of established bacteriuria in one patient on admission was not included. None of the female patients in this group completed their period of catheterisation without having at least one episode of significant bacteriuria. Two patients each had one episode, one patient had 6 episodes and another had 10 episodes, resulting in a total of 18 episodes of significant bacteriuria in the female patients of group B (Table 10).

A total of 727 catheterisations was done on the 4 females. The average incidence of significant bacteriuria in these patients was one per 40 catheterisations, *i.e.* overall 2.48% of catheterisations resulted in an episode of significant bacteriuria in female patients of group B (Table 10).

Effect of Kanamycin-Colistin Bladder Instillations on Incidence of Significant Bacteriuria During Intermittent Catheterisation

Male Patients The mean incidence of significant bacteriuria during intermittent catheterisation of male patients not receiving bladder instillations of kanamycin-colistin at the end of each catheterisation was 1.43% (Table 8). When these instillations were given, the incidence was approximately one-half, *i.e.* 0.75% (Table 7) ($P<0.05$). Of the 21 male patients who did not have kanamycin-colistin instillations, only 2 did not have any episodes of significant bacteriuria during their course of intermittent catheterisation (Table 8). In contrast, 9 of the 17 males who received kanamycin-colistin instillations did not have an episode of significant bacteriuria during the period of catheterisation (Table 7) ($P<0.025$).

Female Patients The mean incidence of significant bacteriuria during intermittent catheterisation of female patients not receiving bladder instillations of kanamycin-colistin was 2.48% (Table 8). However, only one-half of this incidence occurred when these instillations were given, *i.e.* 1.07% (Table 9) ($P<0.05$). All of the 4 females who did not receive the instillations had at least one episode of significant bacteriuria (Table 8), whereas 2 of the 5 females who had the instillations did not have any episodes of significant bacteriuria (Table 9). In this respect the females showed a trend in the same direction as the males, but the number of female cases was too small to be statistically significant.

Micro-organisms Which Caused Significant Bacteriuria During Intermittent Catheterisation

The micro-organisms which were cultured from the catheter specimens of urine while the patients were being intermittently catheterised are listed in Table 11 (male patients) and Table 12 (female patients).

There was no significant difference in the pattern of organisms isolated from males and females.

The organism most frequently cultured from the urine of patients not receiving kanamycin-colistin bladder instillations was *Klebsiella* species which was responsible for 20 (31%) of the 64 episodes of significant bacteriuria in males and 7 (39%) of the 18 episodes in females. All of the isolates of *Klebsiella* spp. were sensitive to both kanamycin and colistin, and this organism did not cause any episodes of significant bacteriuria in patients receiving kanamycin-colistin bladder instillations. In patients receiving the instillations, *Staph. epidermidis* replaced *Klebsiella* spp. as a common cause of significant bacteriuria, accounting for 7 (35%) of the 20 episodes in males and 5 (45%) of the 11 episodes in females. All but one of the strains of *Staph. epidermidis* were resistant to both kanamycin and colistin. *Str. faecalis,* which was resistant to both kanamycin and colistin, was a common cause of significant bacteriuria in both males and females receiving and not receiving kanamycin-colistin bladder instillations.

Table 11 Micro-organisms which Caused Significant Bacteriuria During Intermittent Catheterisation of Male Patients

Group	*Micro-organism*	*Number of episodes of significant bacteriuria*	*Antibiotic sensitivities*			
			Sensitive to both kanamycin and colistin	*Sensitive to kanamycin; resistant to colistin*	*Resistant to kanamycin; sensitive to colistin*	*Resistant to both kanamycin and colistin*
A	*Str. faecalis*	10	-	-	-	10
	Staph. epidermidis	7	-	1	-	6
	Proteus mirabilis	1	-	-	-	1
	Providence B	1	-	-	-	1
	Kurthia species	1	-	-	-	1
	Total	20	-	1	-	19
B	*Klebsiella* species	20	20	-	-	-
	Str. faecalis	18	-	-	-	18
	Providence B	6	-	4	-	2
	Staph. epidermidis	5	-	1	-	4
	Acinetobacter anitratus	4	2	-	2	-
	Proteus mirabilis	3	-	2	-	1
	Enterobacter species	2	2	-	-	-
	Enterobacter agglomerans	1	1	-	-	-
	Pseudomonas aeruginosa	1	-	-	1	-
	Pseudomonas fluorescens	1	-	-	-	1
	Staph. aureus	1	-	1	-	-
	Serratia liquefaciens	1	-	1	-	-
	diphtheroid	1	-	-	-	1
	Total	64	25	9	3	27

Table 12 Micro-organisms which Caused Significant Bacteriuria During Intermittent Catheterisation of Female Patients

Group	*Micro-organism*	*Number of episodes of significant bacteriuria*	*Antibiotic sensitivities*			
			Sensitive to both kanamycin and colistin	*Sensitive to kanamycin; resistant to colistin*	*Resistant to kanamycin; sensitive to colistin*	*Resistant to both kanamycin and colistin and colistin*
A	*Staph. epidermidis*	5	-	-	-	5
	Str. faecalis	4	-	-	-	4
	Candida species	2	-	-	-	2
	Total	11	-	-	-	11
B	*Klebsiella* species	7	7	-	-	-
	Str. faecalis	4	-	-	-	4
	Esch. coli	3	3	-	-	-
	Pseudomonas aeruginosa	2	-	-	2	-
	Staph. epidermidis	1	-	-	-	1
	Candida albicans	1	-	-	-	1
	Total	18	10	-	2	6

Effect of Kanamycin-Colistin Bladder Instillations on Types of Micro-organisms Causing Significant Bacteriuria During Intermittent Catheterisation

There was a marked difference in the antibiotic sensitivities of micro-organisms isolated from the urine specimens of patients not receiving kanamycin-colistin bladder instillations compared with those receiving the instillations.

In patients not receiving the instillations a large proportion of the organisms causing significant bacteriuria were sensitive to kanamycin and colistin, *i.e.* 37 (58%) of the 64 isolates from males and 12 (67%) of the 18 isolates from females were sensitive to at least one of the components of the kanamycin-colistin solution. However, in patients receiving the instillations all but one of the total of 31 isolates from both males and females were resistant to both kanamycin and colistin, and one was sensitive only to the kanamycin component of the kanamycin-colistin solution (Tables 11 and 12).

Follow-up

There was no significant difference in the incidence of significant bacteriuria on follow-up after discharge from hospital in the patients in either group A or group B compared with that previously reported from the Perth Spinal Department (Pearman, 1976).

Discussion

Since the incidence of significant bacteriuria during intermittent catheterisation of both males and females receiving kanamycin-colistin bladder instillations was only one-half the incidence of those not receiving the instillations, it is recommended that patients should have these instillations when they are being intermittently catheterised. When intermittent catheterisation is being performed frequently (*e.g.* every 6 h), kanamycin-colistin solution is recommended rather than an aqueous solution of chlorhexidine digluconate 1 in 5000, because this strength of chlorhexidine causes erosive cystitis and haematuria when it is used frequently or for prolonged periods (McFadyen and Simmons, 1968; Pearman, 1971; Harper and Matz, 1975, 1976). However, the recent experimental work of Harper and Matz (1976) has shown that kanamycin base 150 mg and colistin base 30 mg with methyl hydroxybenzoate 0.1% (w/v) in 25 ml of water or normal saline causes erosion of the bladder mucosa of rats. In view of these observations it was decided to reduce the concentrations of the constituents to one-third of those previously used, *i.e.* kanamycin base 50 mg and colistin base 10 mg in 25 ml of water, and also to delete the small amount of methyl hydroxybenzoate preservative from the solution. This modified kanamycin-colistin solution has been used in all patients having intermittent catheterisation in the Perth Spinal Department since 1 February 1978. However, it must be emphasised that *kanamycin-colistin bladder instillations should be used only when intermittent catheterisation is being practised.* It should *not* be given with indwelling catheters because resistant strains of micro-organisms rapidly emerge when it is used with indwelling catheters.

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Effect of Intravesical Formalin on the Urothelium

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Summary—In an experimental study, the urinary bladder of the rabbit was subjected to 10% formaldehyde instillation for periods ranging from 15 to 90 min. Varying degrees of cystitis, ranging from focal superficial to transmural necrotising cystitis, epithelial sloughs and intra-epithelial calcification may be seen. The depth of reaction was related approximately to the duration of exposure. Saline irrigation after instillation, contact time of 10 min and 1% formaldehyde seemed to reduce complications.

Formalin has been used clinically to control severe haemorrhage from primary or secondary tumours of the urinary bladder or from haemorrhagic cystitis following radiation and/or cyclophosphamide therapy (Brown, 1969; Firlit, 1973; Javadpour and Barakat, 1973; Kumar *et al.*, 1975). The purpose of this study was to define the changes in the rabbit urinary bladder caused by intravesical formaldehyde (Formalin).

Materials and Methods

Fourteen male New Zealand white rabbits, weighing between 2.3 and 4.5 kg, were used. General anaesthesia was given to one rabbit and a 10 FG Robinson catheter was passed into the urinary bladder through the urethra with aseptic precautions. Saline was introduced into the bladder by gravity to determine the maximum bladder capacity, which averaged 65 ml. The animal was sacrificed to serve as a control.

A second rabbit was similarly anaesthetised, catheterised and the bladder was filled to about 80% of its capacity (50 ml) with 10% formaldehyde solution. The catheter was clamped and the formaldehyde allowed to remain in the bladder for 75 min. The bladder was then exposed through a midline extraperitoneal incision, opened anteriorly and a partial cystectomy was performed. The bladder was closed in 2 layers with 3/0 chromic catgut sutures and the incision was closed with the same material. The bladder specimen was divided, one-half was preserved in 10% formaldehyde and the other in 95% alcohol to determine changes due to the use of different fixatives. The animal died on the seventh post-operative day. The bladder, ureters and kidneys were removed and fixed in 95% alcohol and 10% formaldehyde.

A group of 6 rabbits had intravesical formaldehyde (10%) instillation for 15 min as described above and were sacrificed 6, 12, 24, 36, 48 and 72 h after instillation.

Three pairs of rabbits were subjected to 10% formaldehyde instillations for 30, 60 and 90 min respectively. One of each pair was sacrificed after 2 days. Autopsies were performed and sections of the bladder and kidneys were prepared and stained with hematoxylin and eosin.

Results

The weight loss ranged from 50 to 300 g in a period of 2 days to 2 weeks. Gross haematuria occurred in all animals after formaldehyde instillation and 3 animals had urinary retention. Bleeding had stopped from the one animal sacrificed at 2 weeks. No change in bladder capacity (as determined by the method described before) was noted up to 2 weeks following formaldehyde instillation. All bladder specimens removed up to 3 days after instillation showed varying degrees of oedema, hyperaemia and haemorrhage (Fig. 1). Necrotic areas were seen in 2 bladders. Perforation of the bladder dome with peritonitis was seen in one animal and in another small bowel mesentery was adherent to the bladder wall. The latter animal also showed extensive intra-epithelial calcification macroscopically (Fig. 2). Dilated ureters were seen in 2 animals, unilateral in one, bilateral in the other.

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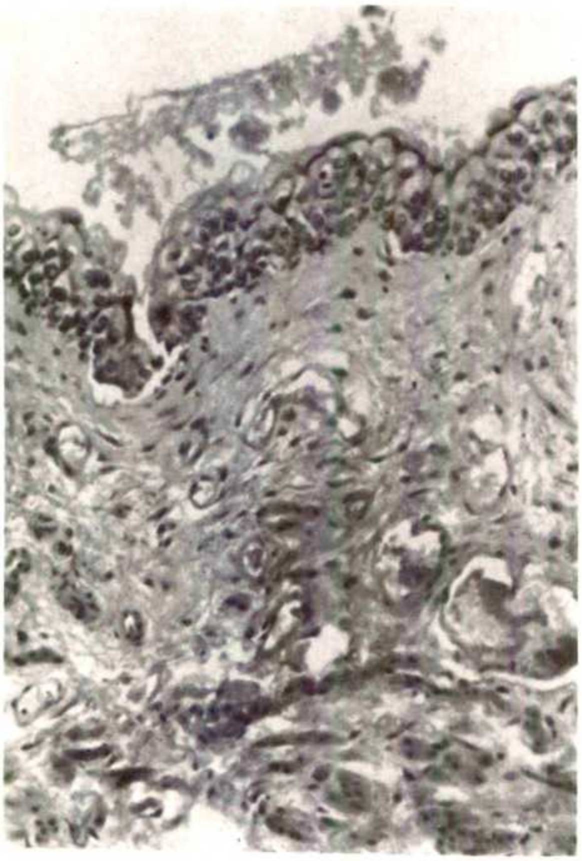

Fig. 1 Bladder showing oedema, hyperaemia and haemorrhage (H and E ×500).

Histologically acute inflammation of peri-ureteric tissue near the renal pelvis and mild inflammatory atypia of the epithelium were seen in the animal which had one grossly dilated ureter and renal pelvis. The bladder of one animal showed focal superficial haemorrhagic cystitis (Fig. 3) and that of another transmural necrotising cystitis. Three animals died; in 2 the bladder was necrotic, in the other perforated. A fourth death was due to an accidental injury.

Discussion

Javadpour and Barakat (1973) did not see any immediate gross or histological changes in the mouse bladder filled with 10% formaldehyde solution for 15 min. In our study, however, the bladders showed varying degrees of oedema, hyperaemia and haemorrhagic areas within 2 days of instillation with 15 min of contact with formaldehyde. This seemed to be due to the chemical

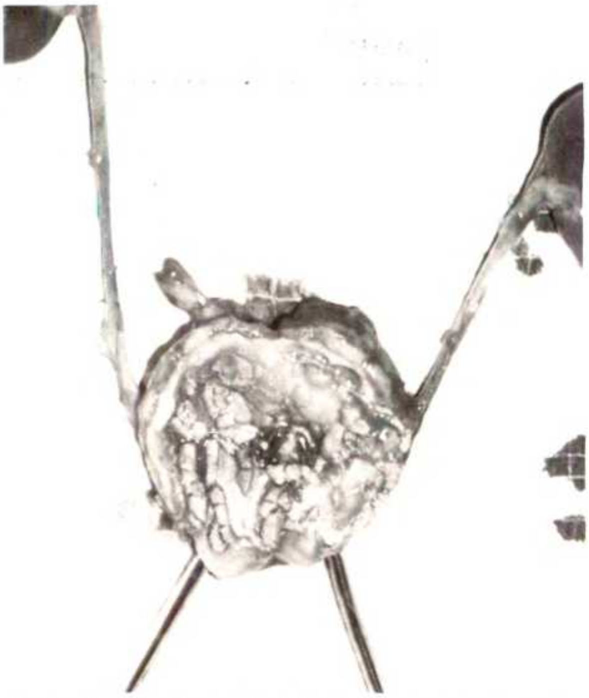

Fig. 2 Extensive intra-epithelial calcification (macroscopic).

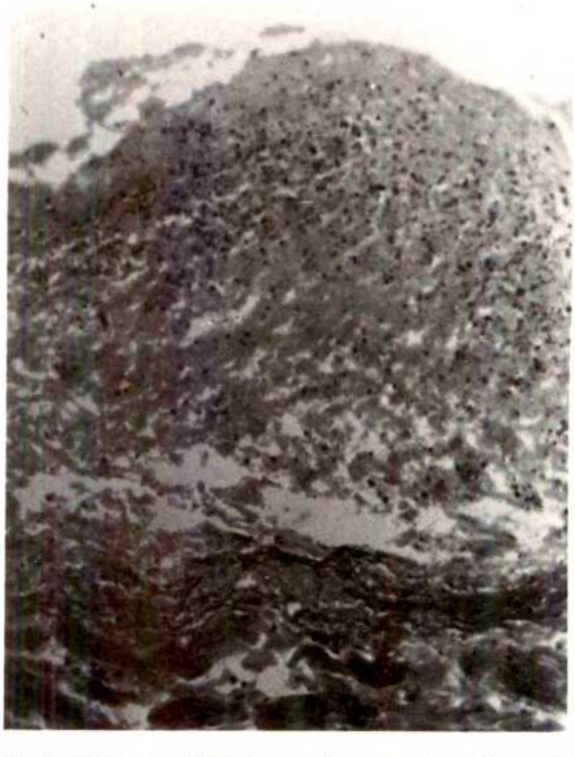

Fig. 3 Focal superficial haemorrhagic cystitis (H and E ×500).

necrosis of the epithelium and underlying connective tissue. Necrosis and perforation of the bladder along with peritonitis were noted between 2 and 6 days, but in these cases a 10% formaldehyde solution was used for 15 to 90 min. Histological study of these specimens revealed that the depth of chemical necrosis was related approximately to the duration of exposure. Thereafter, acute inflammatory reaction developed. The epithelium sloughed and there appeared to be some clotting in superficial blood vessels; this probably accounts for the fact that bleeding can sometimes be controlled with formaldehyde. A recent study in dogs has shown generalised sloughing of the epithelial tissue with the deposition of an amorphous substance, perhaps protein (Whittaker and Freed, 1975). They also noted telangiectasia, vesicoureteric reflux, radiographic evidence of deep bladder ulcer and early bladder rupture. Microscopically they noted intense inflammatory reaction with the deposition of an amorphous substance below the urothelium.

The bladder then appeared to heal by the regeneration of apparently normal urothelium. In one animal intensive macroscopic intra-epithelial calcification was noted 2 weeks after instillation. The fixative nature of formaldehyde seems to affect the necrotic tissue and exudate in the bladder and control haemorrhage due to toxic telangiectasia (Javadpour and Barakat, 1973).

Some of the other findings, such as urinary retention and dilated ureters, are presumably secondary to the oedema and/or vesicoureteric reflux. However, others (Whittaker and Freed, 1975) did not report upper tract changes even in dogs having post-instillation reflux. They irrigated the dog bladder with copious amounts of saline after instillation of formaldehyde and this could explain the lack of ureteric complications. A much reduced complication rate was noted with 1% formaldehyde (Fair, 1974). The use of formaldehyde in the human bladder with an incompetent ureterovesical junction, however, has been associated with papillary necrosis (Kalish *et al.*, 1973), bladder rupture (Scott *et al.*, 1974) and irreversible bilateral ureteric obstruction (Fishbein *et al.*, 1974).

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Comparative Study of the Iglesias Technique and the Suprapubic Drainage Technique for Transurethral Resection

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Summary—Previously we presented a method of suprapubic vesical drainage in which the irrigation fluid was continuously drained from the bladder during transurethral resection of the prostate gland. This method has now been compared to the Iglesias procedure of continuous irrigation. Twenty patients were used for the study, which measured blood loss, intravesical pressure, fluid resorption, operation time and flow of irrigation fluid through the bladder. Bladder pressure was also measured when using different anaesthetics.

The results showed that the operation time was much shorter when the suprapubic technique was used. Bladder pressure during the suprapubic procedure was similar to intravenous pressure but was higher with the Iglesias procedure.

Since McCarthy's resectoscope became available in 1935 the transurethral approach has become increasingly popular in the treatment of prostatic diseases. A substantial technical disadvantage of this method is that the working element must be removed during operation to empty the bladder. This is time-consuming, interrupts the vision and orientation of the surgeon, and causes intermittent higher bladder pressures. This problem appeared to be solved when Iglesias presented his new resectoscope (Iglesias *et al.*, 1975).

A procedure using a suprapubically inserted trocar (Bergman, 1971; Adair, 1972; Reuter *et al.*, 1978), was abandoned because the system was easily occluded.

However, a method of suprapubic vesical drainage has been developed whereby the irrigation fluid can be continuously drained from the bladder. A polyethylene catheter with side holes is inserted through a trocar (Holmquist and Gustavsson, 1975) and left until the next morning for post-operative irrigation. The method has been used successfully with few complications in over 800 operations and we have now compared it with the Iglesias procedure.

Patients and Methods

Twenty patients between 53 and 93 years of age were studied. In 19 cases the diagnosis was benign hyperplasia and in 1 case carcinoma of the prostate. Cystometry with a Semm cystometer was performed pre-operatively and epidural anaesthesia was used.

The pre-operative bladder pressure was measured in 9 patients in order to study the effect of different anaesthetics upon this pressure. The 3 anaesthetic methods studied were epidural, intubation and open mask narcosis.

Suprapubic Drainage Method

After calibrating the urethra to 27 FG, a 26 FG resectoscope (Wolf) was introduced. The bladder was filled via the resectoscope with 300 to 400 ml of fluid (sorbitol 5% + acetic acid 0.25%: Military Chemists, Stockholm) until it was clearly palpable above the symphysis. An 0.5 cm incision was made 2 cm above the symphysis and a modified Reuter's trocar (Wolf 14 FG) was introduced into the bladder (Fig. 1). Through this trocar a 40 cm polyethylene catheter with many side holes (Viggo 3 to 4.5 mm, shortened 5 cm) was introduced and the trocar removed (Fig. 2). The drain was secured with a skin suture and connected via a tube (Medetta 5 mm) to a bucket standing on the floor. This method was used in 12 patients.

Iglesias Method

In 8 patients an Iglesias continuous irrigation resectoscope 26 FG (Wolf) was used.

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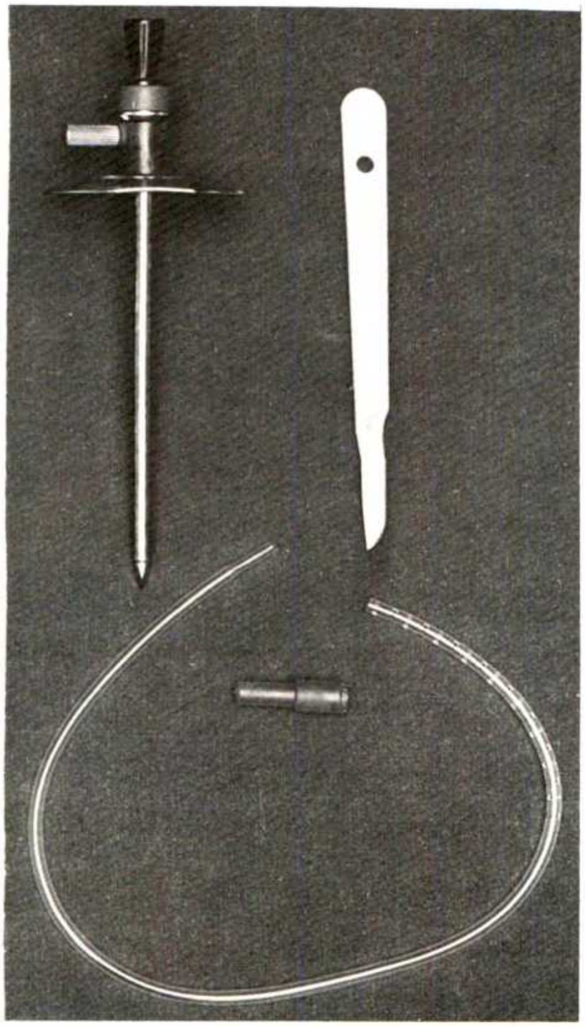

Fig. 1 The equipment, including the trocar and polyethylene tubing.

In both methods the irrigation fluid was siphoned through a one-metre drain into a bucket on the floor. The water pressure of the irrigation fluid was constant at 80 mmHg. An additional catheter, similar to that used for suprapubic drainage, was inserted into the bladder and connected to an electromanometer. The pressure and its variations were recorded on a polygraph (Siemens-Elema, Stockholm).

The blood loss was calculated as follows: a blood sample from the fluid in the bucket was hydrolysed by means of guanidine chloride and with veronal buffer. Thereafter a concentrated haemoglobin reagent was used. The haemoglobin was measured in a viatron-540-spectrophotometer. The result was read against a calibration curve calculated on known amounts of blood.

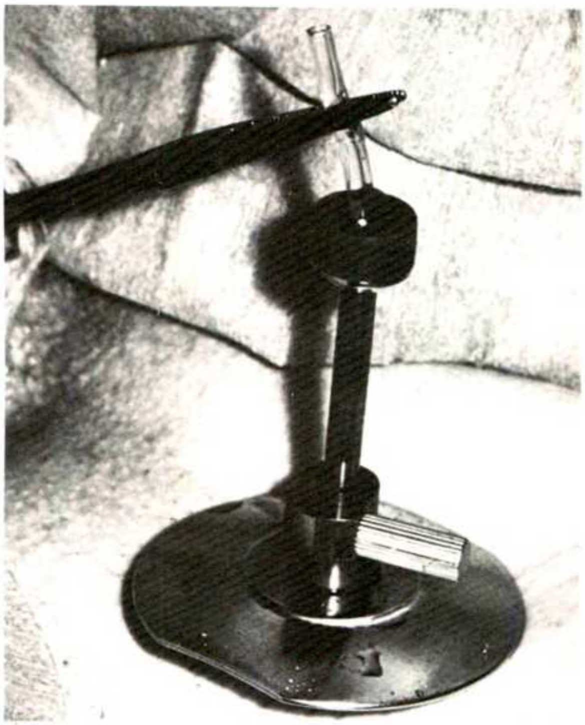

Fig. 2 The trocar inserted and the clamped polyethylene tube introduced into the bladder. After this step the trocar is removed and the tube fixed with a suture.

The resorbed fluid in the patient was calculated in the following 3 ways:

Volumetric method: all fluid into and out of the patient was measured.

Gravimetric method: the patient was weighed before and directly after operation.

In a few cases the isotope ^{123}I-RISA was added to the irrigation fluid.

The urine production was estimated at 10 ml/min during operation.

All fluid losses were collected and measured.

All of the operations were performed by a senior registrar.

Results

Pre-operative cystometry showed the following mean values:

Iglesias method (8 patients) 290 ml. Suprapubic drainage technique (12 patients) 296 ml.

The mean value of the time of operation with the Iglesias technique was 33±11 and with the suprapubic technique 30±11 min.

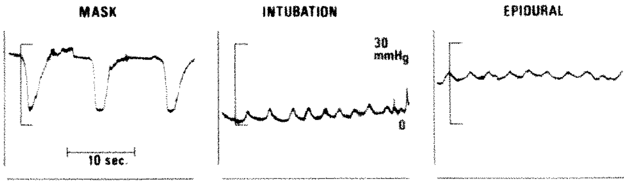

Fig. 3 Bladder pressure variations during 3 different types of anaesthesia.

Speed of resection: Iglesias technique 0.3 g/min. Suprapubic technique 0.6 g/min.

Amount of irrigation fluid used: Iglesias technique 11.9±3.6 litres. Suprapubic technique 15.6±5.8 litres.

Mean flow of irrigation fluid: Iglesias technique 0.4 l/min. Suprapubic technique 0.6 l/min.

Operative blood loss: Iglesias technique 15 to 257 ml (mean 110). Suprapubic technique 6 to 605 ml (mean 180).

Loss of blood correlated to operation time: Iglesias technique 3 ml/min. Suprapubic technique 6 ml/min.

The 3 methods used to measure the resorption of fluid did not correlate and these results are not reported.

The pre-operative intravesical pressure with different anaesthetics is shown in Figure 3.

The intravesical pressure was measured continuously during the operation in 18 patients. The actual figures were determined every 10 min and are shown in Figure 4.

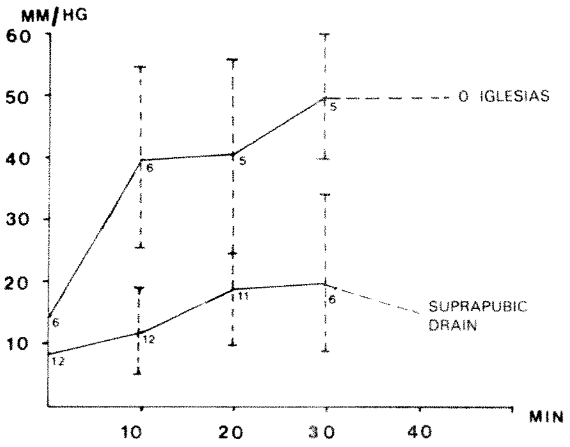

Fig. 4 The bladder pressure was measured on the polygraph paper in 10-min intervals. The figure shows the mean values and standard deviations with the Iglesias method (above) and the suprapubic technique (below) The bladder pressure when using the suprapubic technique does not exceed the central venous pressure.

Discussion

One of the greatest advantages of the 2 techniques is the saving in time. The operation need not be interrupted for emptying of the urinary bladder, the surgeon can work undisturbed, and endoscopic vision is maintained. As a result the procedure is more efficient and bleeding vessels can always be stopped quickly and effectively. This means that more prostatic tissue can be removed per hour.

With the suprapubic technique the drain can be left in position until the following morning to permit effective flushing of the bladder in case of post-operative bleeding, and this facilitates post-operative care. When studying different parameters such as operative time, bleeding, flow and intravesical pressure, we used an inflow pressure of 80 mmHg. This gave a good view of the operative field when using the Iglesias resectoscope but is higher than the inflow pressure recommended by Iglesias.

As a rule it is difficult for the surgeon to estimate blood loss during a transurethral resection because minor bleeding colours the irrigation fluid deep red. In the present study the blood loss ranged from 6 to 605 ml and no blood transfusion was given. The blood loss with the suprapubic technique was greater and might be explained by the increased flow through the urinary bladder. The view was always clearer, and consequently the surgeon did not always spend enough time sealing the bleeding vessels. With the suprapubic technique these vessels must always be sealed, even though the maintenance of adequate visibility does not seem to warrant this. If the bleeding is correlated to the weight of tissue removed, it is found to be the same for both methods.

It has been noted that the so-called transurethral resection syndrome correlates with the intravesical pressure during operation (Madsen and Naber, 1973). High pressure in the prostatic fossa brings an increased risk of this syndrome by the resorption of fluid into the vascular system through opened vessels, mostly veins. The venous pressure is 5 to 10 mmHg and it was clearly shown by Madsen and Naber that the intravesical pressure should be about the same or even lower. When using an isotonic irrigation solution the risk is minimal. The cases investigated in our series did not show any clinical sign of a transurethral resection syndrome or acute heart failure. We tried to measure the patient's increase in weight during operation by means of volumetric and gravimetric methods but inconsistent values were obtained and therefore could not be evaluated. The investigation has, however, shown that bladder pressure during operation is significantly higher with the Iglesias method (Fig. 4). With the suprapubic drainage technique the bladder pressure is usually similar to the venous pressure. It may be concluded that the latter method is safer.

Of the anaesthetic methods investigated, epidural anaesthesia is to be preferred as it produced only minor variations in pressure and intra-abdominal pressure remained extremely stable. With open mask anaesthesia the pressure variations, which were correlated to breathing, amounted to 30 mmHg.

In summary, the following differences were noted when the 2 techniques were compared:

(1) Operation time with the suprapubic drainage technique was about half that of the Iglesias procedure.

(2) More blood was lost with the suprapubic technique but no patient was given a blood transfusion.

(3) The Iglesias method produced bladder pressures between 40 and 50 mmHg; with the suprapubic technique they varied between 10 and 15 mmHg.

(4) It is easier to teach young surgeons the technique of transurethral resection using the suprapubic method.

(5) The suprapubic drainage catheter, left in position until the morning after operation, facilitated post-operative irrigation and eased the patient's post-operative recovery.

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Evaluation of Plasma Hormone Concentrations in Relation to Clinical Staging in Patients with Prostatic Cancer

BRITISH PROSTATE STUDY GROUP*

Summary—Plasma concentrations of testosterone, oestradiol-17ß, luteinising hormone (LH), follicle stimulating hormone (FSH), prolactin and growth hormone (GH) were measured in patients with histologically proven prostatic cancer, before any form of therapy was given for this disease. Patients were categorised according to UICC classification.

No systematic change in the group means of any of these hormones was associated with the progression of the disease from the T0 to the T4 stage. When multivariate analysis was applied to the combined intraprostatic (T0 + T1 + T2) and extraprostatic (T3 + T4) tumour category in patients without clinically evident metastases (M0) a discrimination was observed, GH substantially contributing to the separation of the 2 groups.

When plasma hormone data from patients classified as M0 (without metastases) were compared with M1 patients (with metastases), mean GH values were significantly larger ($P<0.02$) in patients with metastases. GH was also a major contributory factor to the discrimination between the M0 and M1 groups, using multivariate analysis. Testosterone group means for M0 versus M1 were also significantly different ($P<0.02$).

The basis of most endocrinological studies concerning the prostate gland has been the fact that its growth, maintenance and functional activity are largely dependent upon androgenic hormones secreted by the testes. The clinical behaviour of prostatic cancer also reflects androgen stimulation, although the endocrine factors concerned with the aetiology of the disease are little understood. It may well be that the hormonal role in the pathogenesis of prostatic cancer is more permissive than inciting, for present knowledge offers few leads that relate hormonal factors with the initiation of the condition.

Clinical data indicate that carcinoma of the prostate in man is, to some extent, functionally dependent upon androgenic stimulation and it is well established that the incidence of the disease increases with age during the period when testicular activity is declining. Although Kent and Acone (1966) reported that the plasma concentration of testosterone is maintained at a relatively constant level from the age of 20 to the ninth decade, this resulted from a decrease in the metabolic clearance rate of the hormone rather than from a sustained ability of the testes actively to synthesise and secrete testosterone. Conversely, studies by Vermeulen *et al.* (1972) and by other groups (Giusti *et al.*, 1975; Baker *et al.*, 1976) tend to suggest that plasma testosterone levels decrease with ageing, particularly after the sixth decade. This change, therefore, together with the observed increase with age in sex hormone binding globulin and plasma oestradiol-17ß concentration (Pirke and Doerr, 1973) does direct attention to a possible imbalance in the androgen-oestrogen status of elderly men which may be implicated in the aetiology of prostatic disease. However, determination of the androgen and oestrogen levels in patients with prostatic cancer, benign prostatic hyperplasia and in age-matched controls has not shown significant differences between these 3 groups (Moon and Flocks, 1970; Harper *et al.*, 1976; Bartsch *et al.*, 1977).

Furthermore, despite experimental work in animals, which suggested that pituitary hormones may influence prostatic growth and function

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(Lostroh and Li, 1957; Gunn *et al.*, 1965; Laurence and Landau, 1965) there have been few studies on the relationship between plasma protein hormones and prostatic cancer (Asano, 1962; Geller *et al.*, 1970; Harper *et al.*, 1976; Hammond *et al.*, 1977). There is little evidence, for example, that the changing androgen-oestrogen balance can influence circulating FSH, LH or prolactin levels. Although it has been reported (Isurugi *et al.*, 1974) that plasma LH increases with advancing age, the ability of the testis to respond to HCG administration is preserved in the elderly man (Longcope, 1973). Wide and his colleagues (1973), however, were unable to show a change in basal levels of FSH and LH with age, although the capacity of the pituitary to respond to administered LH-RH tended to decrease (Hashimoto *et al.*, 1973; Haug *et al.*, 1974). It has also been reported that there was a comparable prolactin response when thyroid hormone releasing hormone (TRH) was administered to groups of males of different ages (Jacobs *et al.*, 1973), an observation subsequently confirmed by Yamaji *et al.* (1976), who also stated that ageing did not appear to be associated with changes in basal secretion of prolactin.

The present study was undertaken to examine the relationship between hormone levels in the plasma of patients with histologically proven prostatic cancer and primary tumour staging. The presence or absence of metastases was also considered. It is possible that a particular endocrine *milieu* is conducive to the growth and spread of a primary tumour. The influence of prostatic cancer on the endocrine status of the host has also received little attention. Debilitating effects of advanced prostatic cancer have been reported to decrease androgen levels (Robinson and Thomas, 1971) but it is not known if tumour mass, grade or spread, either locally or distally, influence the secretion of hormones such as prolactin, growth hormone or cortisol. This study forms part of a major investigation into the endocrinology of prostatic cancer by the British Prostate Study Group. This group, consisting of urologists from various clinics in the United Kingdom, in association with the Tenovus Institute for Cancer Research, was established to promote co-operative studies on patients classified and managed in a consistent manner. An assessment of differences in the hormone concentrations between the various groups was undertaken using both nonparametric and parametric statistical methods.

Patients and Methods

One hundred and ninety-seven patients with ages ranging from 49 to 93 years were studied. The patients were those who had presented at one of the clinics associated with the Prostate Group and were selected, assessed and classified according to a standardised protocol accepted by the Group.

Patients had histologically proven carcinoma of the prostate and had not previously received any treatment. They were classified according to primary tumour site and metastatic status, using the T and M categories recommended by the Union Internationale Centre Cancer (UICC) (Wallace *et al.*, 1975).

Blood samples, taken in the morning as near as possible to 0900 h, were obtained only after the consent of the patient had been received. Plasma was then stored, deep frozen, until assayed.

Hormone Assays

Total plasma concentration of testosterone was measured by a slight modification of a specific radioimmunoassay previously described (Hillier *et al.*, 1973). Plasma oestradiol-17β was measured by a modified procedure of Cameron and Jones (1972).

Plasma LH and FSH were assayed by a double antibody radioimmunoassay shown to be specific for these hormones (Groom *et al.*, 1971). Plasma GH was estimated by a specific double antibody radioimmunoassay (Schalch and Parker, 1964) using purified human GH (MRC 69/46) and rabbit antiserum to the hormone (Wellcome Reagents Ltd, England). Plasma prolactin was measured by a homologous double antibody radioimmunoassay in which there was a negligible cross-reaction with FSH, LH, TSH, GH and chorionic somatomammotrophin (Cole and Boyns, 1973). The sensitivities of the assay procedures for testosterone, oestradiol-17β, LH, FSH, GH and prolactin were 0.052 nmol/l, 11 pmol/l 0.5 IU/l of MRC 63/15, 0.5 IU/l of 2nd-IRP-HMG, 0.5 mU/l and 0.03 U/l respectively as assessed by the method of Kaiser and Specker (1956), where the value of the constant (k) used in this study was 2.0.

All hormone measurements were undertaken by the Tenovus Institute for Cancer Research. Radioimmunoassay data-processing for the steroid and polypeptide hormones utilised the 4 parameter logistic (Rodbard and Hutt, 1974) and logit-log (Rodbard *et al.*, 1970) models respectively. The quality control procedure used for the polypeptide hormones was that of Shewhart (1931). This technique was also used for the steroid hormones from 1974 until 1976. During the latter period (1976 to 1978) of the survey, the steroid assays have been monitored by more sophisticated cumulative sum

Table 1 Plasma Hormone Concentrations in Patients Classified According to the Primary Tumour Category in the Absence of Metastases (M0)

Patient T category	*Statistic*	*Age (years)*	*Plasma hormone concentration*					
			T (nmol/l)	*E_2 (pmol/l)*	*LH (IU/l)*	*FSH (IU/l)*	*GH (mU/l)*	*Prolactin (U/l)*
T0	Mean	74	14.6	110	5.5	8.1	2.0	0.15
	SD	8.3	5.5	36.8	6.33	6.00	2.36	0.159
	Range	61-82	3.5-24.3	44-151	0.5-19	4-21	0.5-7.0	0.04-0.46
	n	8	8	7	7	7	7	6
T1	Mean	67	13.5	110	8.0	21.0	2.6	0.16
	SD	8.9	6.77	48.9	7.48	25.0	2.0	0.124
	Range	56-80	1.4-22.9	51-195	ND-19	ND-70	1-6	0.02-0.37
	n	9	9	8	8	8	8	8
T2	Mean	71	15.6	125	7.4	15	5.3	0.18
	SD	7.4	7.36	48.5	5.78	10.9	8.89	0.152
	Range	50-82	6.9-27.1	59-254	ND-22	0.5-43	0.5-37	ND-0.52
	n	22	17	17	18	18	16	17
T3	Mean	70	15.3	99	10	14	1.9	0.17
	SD	8.7	5.49	42.3	12.72	15.5	1.96	0.198
	Range	50-88	5.9-30	44.1-184	ND-61	ND-54	ND-9	ND-0.79
	n	34	28	26	25	26	25	25
T4	Mean	64	17.0	96	8.8	23	3.8	0.16
	SD	8.2	3.61	36.0	8.70	39.0	5.12	0.116
	Range	49-79	10.4-20.1	77-165	2-25	2-102	ND-14	ND-0.33
	n	6	6	6	6	6	6	6

T = testosterone, *E_2* = oestradiol-17*β*, *LH* = luteinising hormone, *FSH* = follicle stimulating hormone, *GH* = growth hormone, *SD* = standard deviation, *n* = number of patients, and *ND* = not detectable.

techniques (Kemp *et al.*, 1978; Wilson *et al.*, 1979) that are more suited for assays carried out frequently.

Statistical Analysis

The analysis of clinical and hormone data was performed using techniques similar to those reported previously (Griffiths *et al.*, 1978; Wilson and Tan, 1978). Information from clinical and plasma hormone pro formas was transcribed on to punched cards, verified and then validated for incorrect entries. Data were visually assessed in the form of graphic and histogram displays to establish interrelationships between variates and the nature of frequency distributions as required for multivariate analysis (Krishnaiah, 1969). All statistical analyses were performed on an ICL 4-70 computer.

Results

Plasma Hormone Concentrations in Various Groups of Patients

Plasma hormone concentrations were analysed in relation to the T categories of the prostatic cancer and to the presence or absence of metastases. Values for the plasma hormone concentrations for patients without evidence of metastases (M0) and those with (M1) are shown in Tables 1 and 2 respectively. Data for the comparison of M0 versus M1, irrespective of T category are shown in Table 3. Differences between groups were considered to be significant at the $P<0.05$ level using the Mann-Whitney U test.

The significant difference seen in the testosterone values (Table 2) for the (T0 + T1) group versus the (T3 + T4) group for the M1 category patients was not evident in the corresponding data from the M0 category patients (Table 1). A significant difference $P<0.02$ was observed however, in the testosterone concentrations in plasma from patients separated according to metastatic status, irrespective of T category of the primary tumour (Table 3).

Oestradiol-17ß concentrations exhibited no significant difference either with respect to T category or metastatic status and the same observations were made for LH and prolactin, although a

Table 2 Plasma Hormone Concentrations in Patients With M1 Disease Classified According to Primary Tumour Category

Patient T category	*Statistic*	*Age (years)*	*Plasma hormone concentration*					
			T (nmol/l)	E_2 *(pmol/l)*	*LH (IU/l)*	*FSH (IU/l)*	*GH (mU/l)*	*Prolactin (U/l)*
T0	Mean	74	10.1	158	8.5	13	7.2	0.26
	SD	13.5	8.43	162.1	5.85	15.2	3.83	0.267
	Range	49-93	3.5-27.1	40.430	0.5-16	0.5-33	2-12	0.05-0.67
	n	7	7	5	5	5	5	5
T1	Mean	75	7.3	121	1.9	6.8	1.3	0.19
	SD	3.7	6.0	40.4	1.03	4.11	0.50	0.087
	Range	71-80	1.0-13.2	88-173	0.5-3	2.11	1-2	0.9-0.30
	n	4	4	4	4	4	4	4
T2	Mean	71	13.9	103	6.4	14	2.0	0.19
	SD	5.7	5.35	51.5	5.80	10.9	2.45	0.131
	Range	57-89	5.5-27.9	22-199	0.21	2-41	ND-9	0.05-0.41
	n	26	16	12	11	11	11	11
T3	Mean	72	14.6	111	5.9	13	3.8	0.18
	SD	7.9	6.81	50.8	4.44	16.5	4.06	0.117
	Range	55-87	1.0-29.5	22-239	ND-18	1-95	0.18	ND-0.5
	n	61	52	46	47	47	47	47
T4	Mean	68	12.2	107	6.2	8.6	4.4	0.18
	SD	9.7	6.70	45.6	4.96	12.56	4.4	0.133
	Range	55-90	1.4-29.2	48-199	0.5-17	0.5-59	0.5-16	0.03-0.04
	n	25	20	21	21	20	22	19

T = testosterone, E_2 = oestradiol-17β, *LH* = luteinising hormone, *FSH* = follicle stimulating hormone, *GH* = growth hormone, *SD* = standard deviation, *n* = number of patients, and *ND* = not detectable.

few groups were significant ($P<0.05$) for FSH, *e.g.* T2 versus T3 and T3 versus T4. No progressive changes in any of these hormones could be seen with increasing tumour size.

Data for GH appeared equivocal. Plasma concentrations of GH in groups T2 (n = 16) versus T3 (n = 25) are significantly different in those groups of patients in the M0 category, in which there are relatively large numbers of observations. GH values of the T4 category patients, however, were not significantly different from those of the T2 patients and neither was there a progression of GH values with increasing T category. The data derived from the M0 patients (Table 1) were not

Table 3 Plasma Hormone Concentrations in Patients With Prostatic Carcinoma With and Without Metastases

Patient M category	*Statistic*	*Age (years)*	*Plasma hormone concentration*					
			T (nmol/l)	E_2 *(pmol/l)*	*LH (IU/l)*	*FSH (IU/l)*	*GH (mU/l)*	*Prolactin (U/l)*
Patients with metastases M1	Mean	71	13.2*	114	6.0	11	4.0*	0.19
	SD	8.4	6.18	59.93	4.75	14.7	4.09	0.13
	Range	49-93	1.04-29.5	22.1-430	ND-21	0.5-95	ND-18	ND-0.67
	n	118	99	88	88	87	89	86
Patients without metastases M0	Mean	70	15.3*	107	8.1	15	2.6*	0.17
	SD	8.5	5.97	44.5	9.54	18.2	2.68	0.163
	Range	49-88	1.38-30.2	44.1-254	ND-61	ND-102	ND-37	ND-0.79
	n	79	68	64	64	65	62	62

* $P<0.02$.

T = testosterone, E_2 = oestradiol-17β, *LH* = luteinising hormone, *FSH* = follicle stimulating hormone, *GH* = growth hormone, *SD* = standard deviation, *n* = number of patients, and ND = not detectable.

Table 4 Correlation Tables for Age and Hormone Data

a. Primary tumour—T3 Category

Age	1.00						
T	0.30*	1.00					
E_2	0.23	0.38*	1.00				
LH	0.15	0.14	0.03	1.00			
FSH	0.29*	0.00	0.06	0.52*	1.00		
GH	0.24*	0.20	0.05	0.08	0.14	1.00	
Prolactin	0.11	0.13	0.03	0.10	0.17	0.18	1.00
	Age	T	E_2	LH	FSH	GH	Prolactin

b. Metastatic classification—M0 category

Age	1.00						
T	0.05	1.00					
E_2	0.02	0.28*	1.00				
LH	0.10	0.09	0.07	1.00			
FSH	0.16	0.17	0.11	0.56*	1.00		
GH	0.10	0.13	0.14	0.08	0.14	1.00	
Prolactin	0.01	0.02	0.02	0.18	0.19	0.28*	1.00
	Age	T	E_2	LH	FSH	GH	Prolactin

* $P<0.05$.

T = testosterone, E_2 = oestradiol-17β, LH = luteinising hormone, FSH = follicle stimulating hormone, and GH = growth hormone.

consistent with the corresponding results for the M1 patients, who were also grouped according to T category (Table 2). Plasma GH concentrations appear, however, to be significantly higher at the $P = 0.0239$ level in those patients with metastatic disease (Table 3).

In summary, therefore, with the exception of GH, no differences between hormone concentrations or ages were obtained for the various clinical groups studied.

Interrelationships of Plasma Hormone Values and Age

The product moment correlation tables for plasma hormone concentrations and age were obtained for each group of patients, classified according to their T and M categories. The results for all the various T and M groups were essentially identical and only those obtained for the T3 and M0 categories are shown in Tables 4a and b. Significant values for the correlation coefficient (r) ($P<0.05$) were found for FSH and LH and were 0.51 for T0 (n = 24); 0.67 for T1 (n = 14); 0.72 for T2 (n = 31); 0.52 for T3 (n = 73); 0.81 for T4 (n = 22); 0.56 for M0 (n = 79) and 0.60 for M1 (n = 74). Table 4a also shows that testosterone, oestradiol-17β, FSH and GH correlated reasonably well ($P<0.05$) with age for all T3 category patients. This was not observed from the results shown in Table 4b where all patients in the M0 category were evaluated.

Canonical Variate Analysis

The plasma hormone values, together with the age of the patients in the various clinical groups, were subjected to canonical variate analysis. This type of multivariate statistical analysis can lead to the separation of groups of patients and consequently identifies those variables which are likely to contribute most to the discrimination between the groups (Krzanowski, 1971).

When the hormone concentrations for patients without clinically evident metastases were grouped according to primary tumour T categories (T0 + T1 + T2) versus (T3 + T4) and compared by canonical variate analysis, separation of the variate group means was obtained.

Values for the variate group means for age, testosterone, oestradiol-17β, LH, FSH, GH and prolactin, denoted as X_j ($j = 1, \ldots, 7$), expressed in years, nmol/l, pmol/l, IU/l, IU/l, mU/l and U/l were approximately 71.62 and 69.58; 15.9 and 14.0; 98 and 84; 4.59 and 7.75; 11.39 and 16.96; 2.22 and 0.96; 0.14 and 0.09 respectively. The corresponding loading factors were —0.0223, —0.0363, —0.0172, 0.0571, 0.0302, —0.2495 and —2.5973 and the values for the canonical variate means were —0.49 and 0.6533 respectively. The latent root was significant at the $P<0.05$ level and the discriminant function was of the form:

$$y = 3.6822 + \sum_{j=1}^{7} L_jX_j.$$

GH contributed about 27% to the overall separation of the canonical variate means.

In the case of patients classified into 2 groups based on the presence or absence of metastases, the principal components in the separation of the canonical variate means were age (62%) and GH (31%), the remaining variates contributing very little to the degree of separation. Values for the variate group means were approximately 70.98 and 66.82 (age); 15.2 and 13.9 (testosterone); 92 and 91 (oestradiol-17β); 5.82 and 5.40 (LH); 13.59 and 11.73 (FSH); 1.69 and 2.68 (GH); 0.12 and 0.12 (prolactin) for the M0 and M1 groups respectively. Corresponding values for L_j were 0.1063, 0.0432, —0.004, —0.0264, 0.0054, —0.22 and 0.8906 and the discriminant function was given by the expression:

$$y = -7.1694 + \sum_{j=1}^{7} L_jX_j.$$

The canonical variate means were 0.3181 and —0.3888 for M0 and M1 respectively and the latent root was "significant" at the $P<0.10$ level.

Discussion

Although it is well established that the growth of prostatic tissue is androgen dependent and the clinical behaviour of carcinoma of the prostate indicates that the tumour is dependent upon the secretion of testosterone by the testes, there is little information to suggest that any abnormality in the endocrine status of the elderly man is related to the aetiology of the disease. Previous investigations into the plasma hormone concentrations of patients with prostatic carcinoma have generally failed to produce any marked differences between the determined values and those from normal men or men with benign prostatic hyperplasia (Harper *et al.*, 1976). The present report, concerned with a more detailed survey of hormone levels of patients with untreated cancer in relation to various clinical parameters, has suggested that the use of multivariate analysis of the data may well offer a valuable guide to the interrelationship between the different factors concerned with the disease that are not apparent from the standard statistical treatment of such data.

Since primary tumour staging relates both to tumour size as well as to its intraprostatic localisation, any feedback of steroid metabolic products from the prostatic tissue, on the hypothalamic-pituitary axis, may be expected to be associated with alteration in plasma hormone concentrations as the disease progresses from stage T0 to T4. In the overall assessment of each hormone studied with respect to the different T categories of prostatic cancer, no progressive relationship was evident. Application of multivariate analysis to data from patients without clinically evident metastases produced a discrimination when patients were grouped according to the intraprostatic (T0 + T1 + T2) and extraprostatic (T3 + T4) spread of the primary tumour, with GH contributing most to the separation of the 2 groups.

The protein hormones, LH, FSH and prolactin, would seem to play a minimal role in the discrimination of the primary tumour groups and to be unrelated to the presence of metastatic disease. In animal studies, 5α-reduced metabolites of testosterone were shown to influence gonadotrophin secretion (Swerdloff *et al.*, 1972; Kingsley and Bogdanova, 1973) and it has been reported that the androgen metabolism of a more differentiated carcinoma may differ from that of an anaplastic prostatic tumour (Morfin *et al.*, 1977).

Wide variations in the plasma hormone concentrations were encountered in this extensive study. Many elderly men in their 70s and 80s had plasma testosterone concentrations which were comparable with those of younger men and yet others, aged 50 to 60, had low levels similar to those encountered in oestrogen-treated patients. It is also known that the protein hormones LH and FSH are released in a pulsatile manner and it is well established that stress can influence the secretion of prolactin and GH. Furthermore, although blood was withdrawn between 0900 and 1000 h, variation in hormone values arising from circadian and other time-qualified rhythms (Aschoff *et al.*, 1974) could still exert considerable influence on the statistical conclusions of this survey.

It was of interest, however, that when patients were grouped according to the presence or absence of metastases, GH was the major factor contributing to the separation of the 2 groups. In this study both testosterone and GH were significantly different at a 2% level despite the fact that no progressive relationship was observed with the primary T categories of the cancer.

The use of canonical variate analysis requires that the data are drawn from groups in which the variates are approximately normally distributed and that the variance-covariance matrices of each group are reasonably similar. To ensure that the basic assumptions in the use of canonical variate analysis were not violated, hormone values lying outside ±2 standard deviations from the mean were rejected as "outlying" values. This resulted in a more normal distribution of data. Data rejection must, however, be viewed with some degree of caution but it is pertinent to note that only 5% of the data for each hormone was rejected. Furthermore, GH was still implicated with respect to the above conclusions, when all data were included in the analysis.

These results suggest that the clinical stage of patients with carcinoma of the prostate may, in some cases, be accompanied by differences in their endocrine status and further studies are obviously required to substantiate the observation that GH may be more implicated in the disease than had hitherto been considered. Furthermore, the study has emphasised the potential value of a multicentre investigation to produce data from a large number of patients, clinically assessed in a standardised manner.

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Increased Serum Prolactin Pituitary Reserve in Patients with Prostatic Neoplasms

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Summary—Prolactin (PRL) pituitary reserve was measured in 8 patients with prostatic adenoma and 11 patients with prostatic carcinoma.

The PRL reserve was significantly higher in these patients compared to an age-matched control group of 6 subjects. A possible role for PRL-inhibiting drugs in the management of oestrogen-resistant carcinomas of the prostate is suggested.

A possible role for PRL in the physiological and pathological development of the prostate gland was suggested many years ago (Huggins and Russel, 1946; Grayhack *et al.*, 1955).

At present it is well known that prolactin promotes the affinity of the prostate for testosterone (Farnsworth and Gouder, 1977) and the synthesis of this hormone (Rubin *et al.*, 1976). Furthermore, PRL probably potentiates the enzyme 5 α-reductase, which is indispensable for the conversion of testosterone (T) to dihydrotestosterone (DHT).

It has been shown experimentally that, in castrated animals, the hypertrophic effect of testosterone on the prostate gland was potentiated when PRL was administered (Yamanaka *et al.*, 1975).

However, in the studies by Hammond *et al.* (1977) PRL was shown to increase after the sixth decade in patients with benign hypertrophy, prostatic carcinoma and also the normal age-matched control population; there were no differences in PRL between these 3 groups. These studies were based on basal values for PRL and did not take PRL reserve into account.

In our report we have evaluated PRL secretion in patients with prostatic neoplasms in basal conditions and after stimulation with TRH (thyrotropin releasing hormone).

Patients and Methods

The study was carried out in 19 patients, aged 51 to 70, grouped as follows: 8 affected by prostatic adenoma (group A); 6 with untreated prostatic carcinoma, without clinical evidence of metastases and treated neither surgically nor with hormonal therapy (group B); 5 with prostatic carcinoma, without clinical evidence of metastases and who had undergone, more than 2 months earlier, orchiectomy and therapy with cyproterone acetate in doses of 150 mg/day orally (group C).

Six patients of the same age, free from prostatic pathology and endocrine and metabolic diseases, were also studied as a control group.

A TRH test was carried out in all subjects; this entailed rapid intravenous injection of 200 μg of TRH and venous sampling of blood before and at 10, 20, 30, 45, 60, 90 and 120 min intervals after injection of the tripeptide. Serum samples were stored at −20°C until assayed for PRL content. Hormone levels were measured in duplicate by homologous radioimmunoassay; reagents were supplied by Biodata (Milan) with PRL standard N.I.H.F.I.

The PRL responses to TRH stimulation were evaluated by calculation of secretory areas.

Statistical analyses were performed by Student's *t* test.

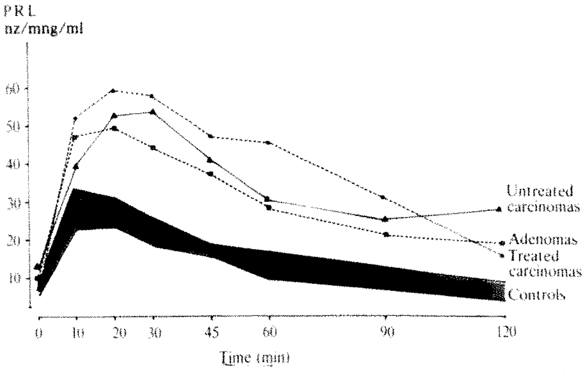

Fig. PRL values observed in various groups of prostatic patients and in the control group during TRH test.

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Table 1 Prolactin Values (X̄ ± SD; ng/ml) Observed in Various Groups of Prostatic Patients and in the Control Group During TRH Test

Time (min) of samples							
0	*+10*	*+20*	*+30*	*+45*	*+60*	*+90*	*+120*
Group A: Adenomas (n = 8)							
9.4	47.0	49.1	44.0	37.7	28.4	22.0	18.8
±5.2	±17.5	±13.2	±12.7	±12.0	±7.9	±4.4	±6.9
Group B: Untreated carcinomas (n = 6)							
12.5	39.5	52.5	53.3	40.6	30.4	25.6	27.8
±7.9	±18.7	±32.6	±31.3	±25.1	±15.9	±15.9	±21.9
Group C: Treated carcinomas (n = 5)*							
7.4	52.2	59.2	45.2	56.8	45.4	31.6	15.6
±1.7	±7.8	±10.4	±14.7	±19.7	±13.5	±11.9	±2.6
Control group (n = 6)							
7.3	28.4	26.8	22.8	17.5	14.7	10.1	7.2
±0.9	±5.0	±3.5	±3.4	±1.2	±3.3	±3.0	±1.9

* Orchiectomy and cyproterone acetate.

Results

Plasma prolactin values are shown in Tables 1 and 2 and in the figure. From these it is evident that the PRL reserve elicited by TRH stimulation was greater in all groups of patients with prostatic disease than in the control group. Also, the total prolactin secretion capacity, indicated by the incremental secretion areas (Table 2), was significantly higher in groups of patients with prostatic disease than in controls ($P<0.05$ — $P<0.01$).

Discussion

This study demonstrated that patients with adenoma or carcinoma of the prostate have a higher pituitary reserve than control patients ($P<0.01$).

Serum PRL levels in patients with prostatic cancer treated by orchiectomy and cyproterone acetate were no different from those in patients with adenomas and patients with untreated carcinomas.

Table 2 PRL Secretion Areas (X̄ ± SD; ng × min) in Various Groups of Prostatic Patients and in the Control Group after TRH

Group A:	2625 ± 1160*
Group B:	2586 ± 775*
Group C:	3878 ± 1296†
Controls:	1004 ± 308

* $P<0.05$.
† $P<0.01$.

They were, however, significantly greater than the serum prolactin levels of patients in the control group.

In view of the increased prolactin capacity of the pituitary gland in patients with prostatic cancer, it is suggested that a possible place should be considered for prolactin-inhibiting drugs, such as L-Dopa or Bromocriptine, in the treatment of prostatic cancer. A recent report by Farnsworth and Gouder (1977) claims good results following administration of Levodopa in patients with prostatic carcinoma that was resistant to anti-androgenic drugs.

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Social Class and Carcinoma of the Prostate

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Summary—Three thousand, six hundred and four patients with carcinoma of the prostate attending the Royal Marsden Hospital, St Peter's Hospitals and all non-teaching hospitals of the South Metropolitan regions were reviewed. In addition, data from 1869 cases of prostatic carcinoma registered in the 2 South Metropolitan regions with determinable social class were compared with data collected from both teaching and non-teaching hospitals.

Carcinoma of the prostate showed an increased incidence with decreasing socio-economic class.

Despite the fact that the prostate is the fourth commonest site for cancer affecting males in England and Wales (Skeet, 1976) the aetiology of this tumour remains unknown. An association has been demonstrated with a variety of factors but only the fact that there is an increasing incidence with age is fully accepted. There is a striking geographic variation with highest age-adjusted mortality rates in Sweden, Switzerland and Norway and lowest in Taiwan, the Philippines and Japan (Hutchinson, 1976).

The relationship between prostatic carcinoma and social class is still the subject of debate. King *et al.* (1963) found no relationship but Richardson (1965) and Ross *et al.* (1979) found a higher incidence of prostatic carcinoma in a higher social class of patients.

Our study was undertaken to establish the relationship between prostatic carcinoma and the different social classes in southern England. The observation of an increased incidence of carcinoma of the prostate in doctors and dentists by King *et al.* (1963) prompted an analysis of these groups in the Cancer Registry data.

Patients and Methods

The study was carried out using data from the South Thames Cancer Registry and from a special study of patients attending the St Peter's group of hospitals. The data from both sources related to the years 1970 to 1975 and were analysed with respect to referral patterns and social class.

Cancer Registry data for the years 1958 to 1974 were used in an analysis of the incidence rates in relation to social class; cases for which no social class could be determined were excluded, together with cases outside the age range of 15 to 64 years. The number of cases in each group is shown in Table 1.

Results

1970 to 1975 Group

In patients attending the specialist teaching hospitals, the social class distribution tended to be biased towards a larger proportion of cases in the higher social classes. Comparing classes I and III in Table 2, social class III exceeded class I by a factor of almost 10 in the non-specialist hospitals, by less than a factor of 5 in the Royal Marsden data and by less than a factor of 2 in the St Peter's group. The data are grouped in Table 3 for which $\chi^2 = 65$ (2 d.f. $P<0.001$).

1958 to 1974 Group

The "Incidence Rates" for cancer of the prostate

Table 1 Sources of Material

Period	*Cases*	*Source*
1970-1975	463	St Peter's Group
	104	Royal Marsden Hospital
	3037	Non-specialist teaching hospitals
1958-1974	1869	Residence in S.E. or S.W. Metropolitan Regions with determinable social class and in age group 15-64

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Table 2 Number of Patients in the Different Social Classes Attending Teaching or Non-teaching Hospitals

Hospitals	I	II	III	IV	V	*Unrecorded*	*Total*
Patients attending the Royal Marsden Hospital	7	20	34	7	5	31	104
Patients attending St Peter's Group Hospitals	88	81	124	54	12	104	463
Patients attending all non-teaching hospitals of the 2 South Metropolitan Regions	93	399	920	349	144	1132	3037

in men under 65 for this 17-year period are shown in Table 4.

(The incidence rate is calculated as follows:

$$\text{Incidence rate} = \frac{\begin{array}{c}\text{Mean annual number}\\ \text{of registrations of}\\ \text{carcinoma of prostate}\\ \text{aged 15-64 for whom}\\ \text{social class could be}\\ \text{determined}\end{array}}{\begin{array}{c}\text{Economically active}\\ \text{male population,}\\ \text{excluding armed forces}\\ \text{and those in}\\ \text{inadequately described}\\ \text{occupations}\end{array}} \times 100{,}000$$

While this value is not meaningful in absolute terms, it serves as an indication of relative prevalence for each social class group.)

Table 3 Number of Patients Attending Teaching or Non-teaching Hospitals, Grouping Social Classes I and II, and IV and V

Hospitals	I/II	III	IV/V
Patients attending the Royal Marsden Hospital and St Peter's Group	196	158	78
Patients attending all non-teaching hospitals of the 2 South Metropolitan Regions	492	920	493

It will be seen that in Table 4 the incidence rate rose from 4.1 per 100,000 in social class I to 10.3 per 100,000 in social class V.

It was also seen that the incidence of carcinoma of the prostate in doctors and dentists in these Cancer Registry data showed a significant increase compared with the expected incidence within class I (Table 5).

Discussion

This study has indicated a strong trend of incidence of carcinoma of the prostate with decreasing social class. The major concern in this and in similar studies is the reliability of the registration and clinical data from which these conclusions are drawn. In approximately one-third of registrations of cancer of the prostate, the occupation was insufficiently explicit to allow a social class group to be determined. It is just possible that if this third were distributed in an unexpected way then the trend seen in this study might disappear. Because of a possible irregular distribution of the "unknown" social classes, these were omitted rather than proportionately distributed among the 5 classes.

Table 4 The "Incidence" of Carcinoma of the Prostate in 1,708,530 Economically Active Male Patients of the 2 South Metropolitan Regions (1958-74)

	I	II	III	IV	V
*Economically active male population (15-64 years)	123,330	380,690	828,520	263,680	112,310
Number of patients in the population with carcinoma of the prostate	87	349	913	323	197
† "Incidence rate"/100,000 per annum	4.1	5.4	6.5	7.2	10.3

* From 10% sample, Census 1971 (Office of Population Censuses and Surveys).

† See definition in text.

Table 5 Registrations of Carcinoma of the Prostate in Social Class I (1958-74).

All Class I	*Observed*		**Expected*		$\dagger\chi^2$	
	Doctors	*Dentists*	*Doctors*	*Dentists*	*Doctors*	*Dentists*
501	61	24	36	8.5	17.4	28.3

* Expected numbers based on 7.2% of social class I being doctors, 1.7% being dentists (Census 1971, 1% sample).

$\dagger\chi = \dfrac{(\text{observed} - \text{expected})^2}{\text{expected}}$ with 1 degree of freedom.

In coding social class from occupation data, Office of Population Censuses and Surveys (O.P.C.S.) procedures were followed. Social class is defined by occupation and status (*i.e.* whether manager, foreman, "worker", etc.) according to the conventions adopted by the General Register Office for the 1961 and 1971 censuses. While in general the correspondence between social class and occupation is good, there are some occupations for which it is difficult to assign a social class. For example, "Company Director" is assigned to social class II but patients thus described range from directors of large multinational companies to self-employed manual workers.

The increase in incidence with decrease in social class may be linked with a variety of factors such as hygiene or sexual habits. Evidence has recently emerged on the relationship between sexual activity and venereal transmission in patients with prostatic carcinoma. Centifanto *et al.* (1972), who found genital herpes virus (type 2) in the male genitourinary tract in the absence of overt disease, later demonstrated this virus in prostatic cells in patients with carcinoma of the prostate (Centifanto *et al.*, 1973). Schuman *et al.* (1977) have found an increase in antibody titre for both this virus and cytomegalovirus in patients with carcinoma of the prostate.

Such findings resemble those described in patients with carcinoma of the cervix. Rawls *et al.* (1969) in a controlled study found that 20% of patients from low social classes had antibody to genital herpes virus type 2. A higher antibody titre was found in prostitutes compared with the general population. Royston and Aurelian (1970) have also shown an increase in antibody titre to genital herpes type 2 with decreasing socio-economic class and produced data to support the suggestion that genital herpes virus may be responsible for the induction of squamous carcinoma of the cervix.

In 1963 King *et al.* noted an increased incidence of carcinoma of the prostate amongst doctors and dentists. The present study has supported this finding amongst this section of class I. In Table 5 the expected numbers of doctors and dentists are very approximate. It is possible that the doctors with carcinoma of the prostate are under-registered since their notes may not be filed in the general records department, especially if they work or have worked in the hospital in which they were treated. While this increase in certain sections of class I is interesting, it is difficult to explain and we can only speculate on the relationship between this observation and the data that are accumulating on a viral aetiology as discussed above.

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Cavernosography in the Management of Prostatic Cancer

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Summary—Cavernosograms were used in the investigation of 22 patients with prostatic cancer to determine the incidence of venous invasion. There were 21 patients with T3/T4 category tumours and one with a T2 tumour. All but one, a T3 tumour, had the radiological features of periprostatic venous malignant thrombosis.

An attempt was made to correlate these findings with lymphography and tumour grade but no correlations could be made and the clinical relevance of these findings remains uncertain.

An accurate assessment of the local extent of the tumour is essential in the clinical staging and management of patients with prostatic carcinoma.

Bandhari *et al.* (1968) claimed that obstruction and thrombosis of the periprostatic venous plexus would be found in carcinoma of the prostate. Le Gouillou *et al.* (1977) reviewed several unconventional methods of investigation in prostatic carcinoma with special attention to prostatic phlebography; they suggested that venous occlusions indicated local extension of disease.

We report our experience with cavernosograms which have been used to study the periglandular venous pattern in patients with prostatic carcinoma in order to detect evidence of local invasion. We have compared this technique with more conventional investigations.

Materials and Methods

During a 2-year period (1976 to 1977) 98 patients were admitted to our department with a diagnosis of carcinoma of prostate. Twenty-two of these patients, unselected and consecutive, were investigated as follows:

(i) Excretion urography.
(ii) Transrectal needle biopsy.
(iii) Pedal lymphography.
(iv) Cavernosography.

Clinical staging and grading were carried out according to the recommendations of Wallace *et al.* (1975).

All patients underwent similar operative treatment, namely transperitoneal pelvic lymphadenectomy, transvesical prostatectomy and bilateral orchiectomy. These patients were then given stilboestrol 100 mg daily for 20 days, then 1 mg daily indefinitely.

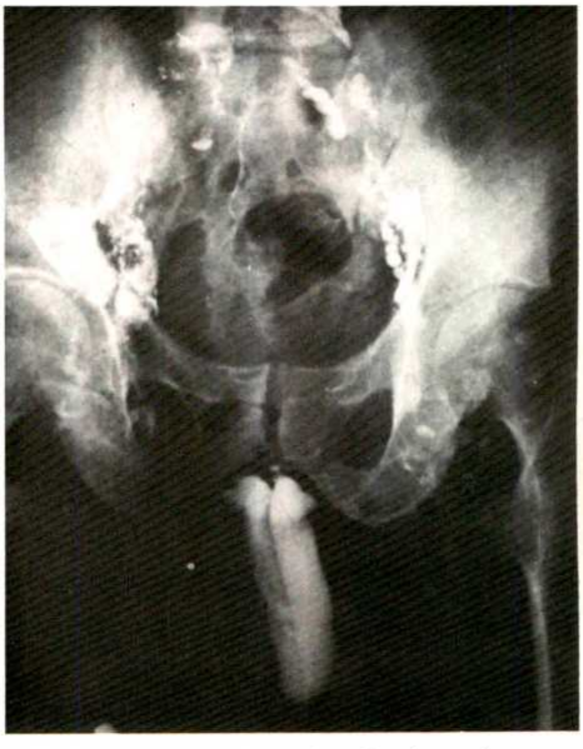

Fig. 1 Case 1. Total obstruction of periprostatic venous drainage. Lymphangiography indicating bilateral lymph node metastases. Surgical and histological confirmation of extraglandular malignant invasion.

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Table

Number	*Clinical staging*	*Grading*	*Lymphangiography*	*Cavernosogram*
1	T3N + M0	3	+	Technical failure
2	T4N + M +	3	+	+
3	T3N + M0	3	+	+
4	T3N0M0	2	–	+
5	T4N0M +	2-3	–	+
6	T3N × M +	1-2	–	+
7	T3N × M0	1	–	+
8	T4N × M0	1	?	+
9	T3N × M0	1	–	–
10	T4N + M0	2-3	+	+
11	T3N + M +	2-3	+	+
12	T4N + M0	3	+	+
13	T2N + M0	2	–	+
14	T3N + M0	1	+	+
15	T4N0M0	1-2	–	+
16	T3N0M0	1	–	+
17	T3N + M0	1	+	+
18	T3N + M0	3	+	+
19	T4N + M0	1	+	+
20	T4N + M0	1	+	+
21	T4N0M0	1	?	+
22	T4N + M0	1	+	+

Lymphangiography: – Normal, + Node involvement.
Cavernosogram: – Normal, + Periprostatic venous involvement.

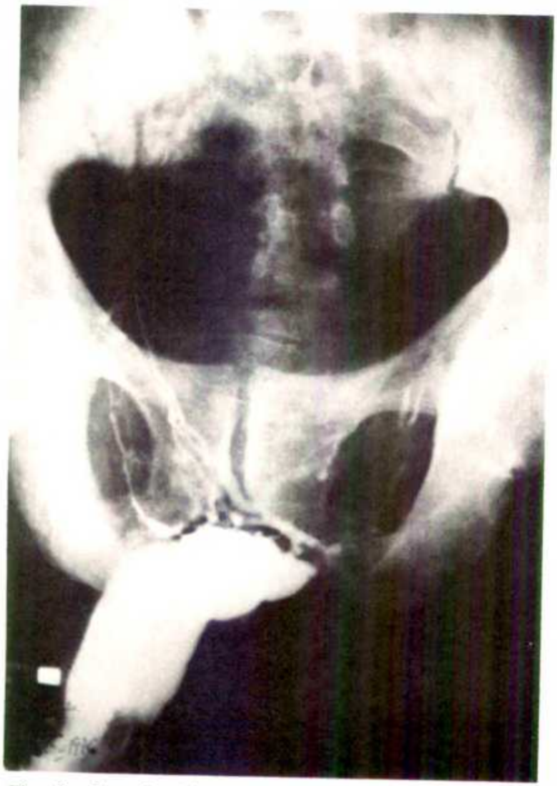

Fig. 2 Case 5. Abnormal cavernosogram. Poor filling of venous return, especially on the left side. Narrow, bead-like chain veins. Extensive pelvic bone metastases.

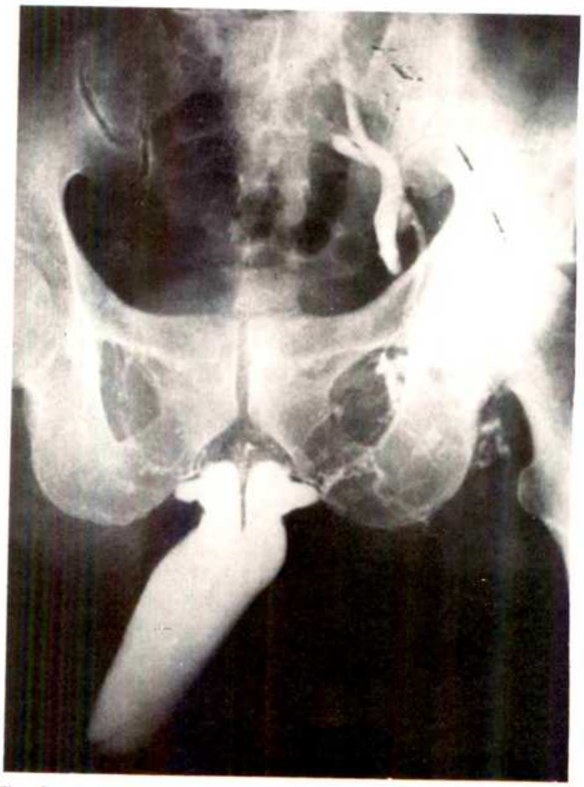

Fig. 3 Case 17. Absence of right periprostatic venous drainage and filling defects on the left, with venous shunts to the saphena magna.

Cavernosography was carried out under local anaesthesia. A No. 1 disposable needle was introduced into the corpus cavernosum on one side, just proximal to the glans. A few millilitres of local anaesthetic were then injected and a free flow, together with the lack of any local swelling, indicated correct placement of the needle; 20 ml of 60% Urografin were then injected via this needle and posterior/anterior views were taken, or direct visualisation on an image intensifier was used.

A compression dressing prevented subsequent local haematoma. There were no complications from this procedure.

The radiological criteria of venous invasion were as follows:

(1) Pooling of dye in the corpus cavernosum and/or retropubically.
(2) Poor or absent periprostatic veins.
(3) Lateral displacement of periprostatic veins.
(4) "Bead-chain" periprostatic veins.
(5) Venous shunts to the saphenous system.
(6) Asymmetry of periprostatic veins.

Cavernosogram findings (positive and negative) were correlated with conventional clinical staging, histological grade and lymphangiography.

Results (Table)

The cavernosograms were positive in 20 cases, there was one technical failure and one was negative. This correlated well with T category as 21 out of 22 patients were thought to have T3 or T4 lesions. The only patients with a T2 lesion had a positive cavernosogram, but normal lymphography and lymphadenectomy.

Seven patients with positive cavernosograms had normal lymphograms but 2 of these were subsequently found to have positive nodes on lymphadenectomy.

Two patients with positive lymphograms and cavernosograms had histologically normal pelvic lymph nodes.

The cavernosogram was positive in all grades of the tumour.

Discussion

The value of the cavernosogram in the management of prostatic carcinoma is uncertain. In previous reports, Drozdovsky *et al.* (1976) obtained useful data for differential diagnosis, assessment of infiltration and detection of venous thrombosis associated with pelvic malignancy. Le Gouillou *et al.* (1977) considered it to be a relatively simple way of detecting the venous anomalies seen in malignancy.

The experience presented in this study is limited to mainly locally advanced prostatic lesions, 4 of which had distant metastases. In these lesions tumour category is more easily assessed by palpation. It would be of interest to assess this technique in less advanced prostatic carcinomas.

Cavernosography did not influence the management of patients in any way, as this was based on the results of more conventional investigations.

It is concluded that insufficient information is available to determine the relevance of a positive cavernosogram in prostatic tumour staging. Without information that can only be obtained by a histological study of the corpora, it must be concluded that this technique adds little to the present methods of tumour staging.

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Scrotal Flap Urethroplasty in the Primary Management of the "Watering-can Perineum"

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Summary—In 12 patients a primary first-stage scrotal flap urethroplasty was used to treat watering-can perinea. The generous scrotal flap is fixed by a single nylon suture to the bladder neck. The method permits better dependent drainage than can be provided by a suprapubic cystostomy.

The scrotal flap urethroplasty (Leadbetter, 1960; Blandy *et al.*, 1968) represents a further advance in the management of difficult posterior urethral strictures. We have modified this technique to meet the challenge of the long, multiple urethral stricture which is complicated by chronic perineal and scrotal fistulae and sepsis—the "watering-can perineum". The condition follows some years after acute gonococcal urethritis or lymphogranuloma venereum, and is often complicated by many false passages. It is seldom possible to establish the exact aetiology when the patient presents himself with a watering-can perineum. In addition to developing all of the complications of lower tract obstructive uropathy, these patients may seclude themselves because of their foul smell.

Materials and Methods

Twelve patients have been treated for a "watering-can perineum" over a 4-year period in the Georgetown Public Hospital, Guyana. Their ages ranged from 48 to 68 years. All had undergone suprapubic cystostomy at some time previously.

The patient was admitted 5 days before operation and given a broad spectrum antibiotic—usually ampicillin. The local region was irrigated with hypertonic saline. Whole blood was kept in reserve.

At the first stage a generous perineoscrotal flap was formed and all woody subcutaneous tissue and pockets of pus excised and flattened. The apex of the flap was attached to the bladder neck by a single monofilament nylon suture. It is important that this suture should take in a good bite of bladder neck. Usually it is possible to insert this suture through the perineal approach, using Turner Warwick's urethral speculum and a modification of his urethroplasty needle whereby the fish-hook bend permits a "push-up/pull-down manoeuvre" to allow a loop of nylon to be caught in a Gillies' skin hook. A finger is passed through the bladder neck to check the position of the scrotal flap as this suture is tied. In one patient it was necessary to open the bladder through a Pfannenstiel incision to insert the suture.

A 24 FG latex Foley catheter was left indwelling for 5 days. The lateral wounds were not sutured, but dressed with tulle gras.

Haemorrhage has been very variable but in only one patient, who had considerable enlargement of the prostate, was it necessary to transfuse 4 units of blood.

The nylon suture was removed after not less than 3 weeks. The unsutured perineal wounds granulated very rapidly and in a surprisingly short time were re-epithelialised. In only 2 of these 12 patients did the perineal sepsis fail to resolve: in one man the appearance resembled hidradenitis suppurativa and the second was readmitted after 5 months with scrotal cellulitis which responded to tetracycline. Both of these men probably had lymphogranuloma venereum.

Second Stage

Only 4 patients were available for a second-stage closure. Two patients were content with the result of the first stage and declined further surgery; 5 others were lost to follow-up and

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it is assumed that they were equally satisfied to void perineally in the squatting position. One had a severe stroke several months after the first stage and was never fit to undergo a second-stage operation.

Induration and loss of elasticity of the perineal skin in these patients made it difficult to form a supple skin tube and we have reverted to the buried skin-strip method as a routine: in all 4 patients secondary revision operations were needed for persistent small fistulae.

There were no deaths in this series and all these men retained urinary continence.

Discussion

By tradition, chronic perineal sepsis is managed by prolonged suprapubic drainage, but this does not always clear up the perineal induration or fistulae, perhaps because it does not afford adequate dependent drainage. The advantage of the present method is 2-fold: not only does it get rid of the underlying stricture, but it also removes much of the infected tissue, opens up the fistulae and the perineal abscesses, and affords excellent dependent drainage.

It should be pointed out that the loss of elasticity of the skin and subcutaneous tissues which results from the prolonged sepsis demands that an unusually generous scrotal flap be formed at the first stage, and makes it necessary to use patience, persistence and ingenuity to reform the urethra at the second stage. However, the results are very gratifying, not least because the patient is enabled to return to society from which for so long he was an outcast.

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Abnormalities of the Suspensory Ligament of the Penis as a Cause for Erectile Dysfunction

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Summary—Four patients are described with a defect of the suspensory ligament of the penis. In one patient this was traumatic in origin but in the other 3 aetiology appeared to be congenital. The clinical history, physical findings and treatment are summarised.

Modern textbooks of urology do not include any description of abnormalities of the suspensory ligament of the penis. The following 4 patients have been seen with erectile dysfunction and represent a well defined clinical entity which may be corrected by a surgical operation.

Case Reports

Case 1

A man aged 32 years presented with impotence. He had no difficulty in obtaining an erection but the penis always protruded at 90° from his body and was so mobile that he was unable to obtain adequate penetration and coitus was impossible. Ejaculation was normal.

The only abnormality which was revealed on physical examination was that 2 fingers could be deeply inserted into the interval between the symphysis pubis and the base of the penis. A cavernogram showed good filling of the erectile tissue but the penis did not rise and remained dependent. A 7 cm transverse lower abdominal incision was made near the base of the penis and absence of the penile suspensory ligament was confirmed. Three nylon anchoring sutures were inserted between the symphysis pubis and tunica albuginea of the penis.

One month later he stated that he had experienced normal erections for the first time in his life and subsequently he reported that coitus was successful.

Case 2

A 25-year-old man complained of impotence since an accident in November 1975 when the penis slipped out of the vagina during coitus and was deflected ventrally with a snapping sound. The next day he noticed a swelling at the base of his penis but there was no bruising. During the next 15 months he was unable to sustain an erection and when erections returned the penis did not assume the normal erect position. Physical examination revealed a defect between the symphysis pubis and base of the penis which would admit 2 fingers.

The base of the penis was explored surgically and 5 nylon anchoring sutures were inserted between the symphysis pubis and tunica albuginea of the penis. Post-operatively he continued to suffer from intermittent episodes of erectile dysfunction but at other times his erections were normal and coitus was possible.

Case 3

A 19-year-old youth was seen on account of erectile dysfunction. He stated that he had a "normal" erection but the penis was unstable and did not point in the correct direction. Ejaculation was normal. He had no difficulty with masturbation but coitus was not possible. He gave no history of any injury and for as long as he could remember the penis had always been unstable at the time of erection.

On clinical examination the only abnormality was that it was possible to place 2 fingers between the symphysis pubis and the penis even when this was held erect.

The patient was admitted for operation and nylon sutures were placed between the symphysis and the tunica albuginea of the penis. The post-operative course was uneventful and the patient has had normal erections. He has not had an opportunity to attempt coitus since the operation.

Case 4

A 25-year-old man presented on account of sexual dysfunction. In response to sexual stimulation he developed an erection but the penis never assumed an erect position and always flopped over towards the left. Ejaculation was normal.

On clinical examination he appeared to have absent tissue between the symphysis pubis and the penis and he was, therefore, admitted for surgical correction.

At operation 4 nylon sutures were placed between the tunica albuginea and the symphysis pubis but when the penis was inflated with saline it failed to assume

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the erect position. The penis in this patient was relatively long and a further row of sutures was placed lower down the shaft towards the glans penis. Subsequent inflation of the corpora with saline resulted in a normal erection.

The post-operative course was uneventful and the patient has reported that he has since had normal erections for the first time in his life. Coitus has been possible.

Discussion

The function of the suspensory ligament of the penis would appear to be one of anchoring the penis so that it enlarges during an erection and assumes a position at an angle of approximately 30° to the anterior abdominal wall. In this position it is relatively rigid and allows coitus to occur. Defects of the suspensory ligament mean that the penis does not assume the normal erect position and although it increases in size it remains unstable. Penetration of the vagina is possible but coitus is extremely difficult as the penis tends to slip out of the vagina.

The diagnosis is made from the description of the abnormality and by clinical examination of the patient. When the defect is present it is possible to place the index and forefingers deeply between the symphysis pubis and penis. It is also possible to demonstrate the deformity by injecting saline, or contrast, into the corpora cavernosa and although the penis enlarges it will not assume the erect position. The correction of the abnormality depends upon placing strong non-absorbable sutures between the tunica albuginea and symphysis pubis but, as demonstrated by the last patient, it is important to check that normal erection occurs and that the mechanical fixation is at such a point as to ensure that the penis erects normally.

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Steroid Therapy in the Treatment of Granulomatous Orchitis

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Summary—Two cases of asynchronous bilateral granulomatous orchitis are presented in which, after initial orchiectomy, successful steroid therapy was instituted.

Case Reports

Case 1

M.G., aged 43, presented with a 6-week history of an influenza-like illness and painful swelling of the left testicle. Initial treatment with tetracycline was unsuccessful. There was no obvious causative factor.

Examination revealed a fit man with a swinging pyrexia and a tender and apparently fluctuant swelling in the left side of the scrotum. Routine investigations, including mid-stream specimen of urine, haemoglobin, full blood count, viscosity, liver function studies and serology were all negative. Urine cultures for TB were subsequently shown to be negative. Chest X-ray and intravenous pyelography were normal.

Exploration of the scrotum revealed a small infected hydrocele and what was thought to be a testicular abscess. An orchiectomy was performed, whereupon his clinical condition rapidly improved and he was discharged one week later to complete a 2-week course of cephalexin. Histology of the excised testicle revealed granulomatous orchitis.

Three weeks later he was readmitted with acute onset of swelling and tenderness in his remaining right testicle. In view of the similarity of symptoms and signs with the previous lesion he was diagnosed as having a recurrence of granulomatous orchitis in the remaining testicle. He was treated with cephalexin 1 g qds and prednisolone 20 mg tds and within 48 h the clinical features had completely resolved. After one week the cephalexin was stopped and he was discharged on a maintenance dose of prednisolone 5 mg tds. Three months later this prednisolone therapy was tailed off and he remains asymptomatic to the present day.

Case 2

S.M., aged 62, presented with a 2-week history of urinary tract infection associated with rigors and an increasing and painful swelling of his right testicle. Treatment with ampicillin produced no obvious improvement.

Examination revealed a tender fluctuant swelling of the right testis.

Exploration of the scrotum suggested a testicular abscess, for which a right orchiectomy was performed. Following this he made an uneventful recovery. Histology revealed the appearance of granulomatous orchitis. Though there were no areas of abscess formation on this occasion, necrotic zones were noted in the excised testicle. Investigations revealed an infected urine but otherwise, as in Case 1, were normal.

Three months later he was readmitted with similar signs and symptoms in his remaining left testis. Following treatment with cephalexin 1 g qds and prednisolone 20 mg tds his symptoms settled within 3 days. He continued on prednisolone 5 mg tds for 3 months. Then the steroid therapy was tailed off and he remained symptom-free for 6 months.

Subsequently he had 2 further recurrences of his symptoms of pain and swelling of the remaining testis, both of which responded to further 3-month courses of steroids. Since the last attack, some 12 months ago, he has had no further trouble.

Discussion

Granulomatous orchitis is a rare condition, usually treated by orchiectomy (Elicker and Evans, 1975). The differential diagnosis of granulomatous orchitis in the United Kingdom should include mumps orchitis, bacterial and tuberculous epididymo-orchitis, sperm granuloma and, most importantly, testicular tumour. The precise aetiology is unknown. Trauma, either direct or following surgery to the urinary tract, may result in the extravasation of sperm which could initiate granulomatous reactions in the testicle and epididymis (Friedman and Garske, 1949; Spjut and Thorpe, 1956). This has been disputed (Glassy and Mostofi, 1956).

Autoimmune reactions to sperm antibodies are not a cause of granulomatous orchitis (Cruick-

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shank and Stuart-Smith, 1959). An association between granulomatous orchitis and urinary tract infection has been described (Lynch *et al.*, 1968) and was the case in one of the 2 patients described above.

Similarities between granulomatous orchitis and sarcoidosis have been stressed (Myburgh, 1956). Steroids are known to counteract chronic granulomatous conditions such as sarcoidosis and this provided the basis of our treatment in these 2 patients. Antibiotic therapy was given to eliminate any urinary infection and as a prophylaxis to prevent secondary sepsis. In neither case was testicular biopsy performed when the patients presented with the second attack in their remaining testicle. This was to prevent any risk of secondary infection following the biopsy and also, on more theoretical grounds, to prevent any worsening of the granulomatous orchitis due to the trauma and possible sperm extravasation that could follow such a procedure. It was felt that the similarities in signs and symptoms with the original and histologically proven granulomatous orchitis in the excised contralateral testis provided enough evidence for the diagnosis in the remaining testis. It is not suggested that steroid therapy should be instituted when doubt exists as to the nature of a testicular swelling but where, as in these 2 cases, there are acceptable clinical grounds for the diagnosis, and where the contralateral testis has already been removed, it would seem that steroid therapy is successful in the treatment of granulomatous orchitis. Such treatment will prevent the need to consider castration.

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Consequences of Vasectomy: an Immunological and Histological Study Related to Subsequent Fertility

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Summary—Studies of 2 groups of patients 2 years and 8 years following vasectomy failed to demonstrate evidence of cell mediated immunity to sperm.

Histological examination of testicular tissue from 11 patients undergoing reversal of vasectomy showed significant abnormalities in each. However, subsequent fertility within 15 months occurred in 7 (63.6%) of these patients.

The nature of the testicular changes and the possible aetiological factors are discussed.

It has been suggested that an immune response to sperm may cause male infertility (Fjallbrant, 1968; Dubin and Amelar, 1971; Rumke, 1972). Although there is, as yet, no definite evidence to support this, sperm antibodies are known to occur in a minority of men with unexplained infertility. It remains uncertain whether these are the direct cause of the infertility or whether they are related to an underlying abnormality of testicular function. Sperm is autoantigenic in man (Mancini *et al.*, 1965) and detectable sperm antibodies develop in approximately 50% of patients following vasectomy (Ansbacher, 1971; Shulman *et al.*, 1972; Van Lis *et al.*, 1974; Tung, 1975).

Patients who undergo technically successful vasovasostomy may exhibit poor fertility subsequently (Hanley, 1968) manifested by oligozoospermia, reduced motility and a high proportion of abnormal forms. It has been suggested (Shulman, 1971) that these effects might be caused by the development of an immune response to sperm after vasectomy.

Testicular lesions are known to develop as a consequence of vasectomy in cats, rats, mice (Cunningham, 1928), guinea pigs (Alexander, 1973; Muir *et al.*, 1976), rabbits (Bigazzi *et al.*, 1976), and man (Gupta *et al.*, 1975). The underlying cause, however, remains unknown.

This study continues the *in vitro* investigation for the development of cell-mediated immunity to sperm after vasectomy, examines the consequent testicular abnormalities, and discusses subsequent fertility following reanastomosis of the vas.

Patients and Methods

All patients were healthy adults. *In vitro* studies for cell-mediated immunity to sperm were undertaken in a total of 42 patients by lymphocyte transformation technique.

Study of 23 patients prior to, and up to 1 year after, vasectomy has already been reported (Muir *et al.*, 1977). Investigation was continued at 4 to 6-monthly intervals to complete a second year following the vasectomy.

The further group of 19 patients had undergone vasectomy 2 to 8 years previously and were similarly investigated for evidence of cell-mediated immunity to sperm. Of these, 11 underwent subsequent vasovasostomy, with testicular biopsy at the time of the reversal, and were followed for restoration of fertility.

Lymphocyte Transformation

The culture technique has been recorded previously in detail (Muir *et al.*, 1977). Briefly, leucocytes from 25 ml of heparinised venous blood were separated on a Hypaque-Ficoll gradient. The cells were cultured with 5 concentrations of a heat-treated extract of human sperm (0.001-10 μg/ml) and with PPD (10 μg/ml) for 96 h at 37°C in 95% air/5% CO_2. The cells were pulsed with 0.5 μCi ^{3}H-labelled thymidine (specific activity approximately 23 Ci/mmol) 4 h prior to

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harvesting. The results were expressed as the Stimulation Ratio (SR):

$$SR = \frac{\text{mean } ^3\text{H-thymidine uptake of cells cultured with antigen}}{\text{mean } ^3\text{H-thymidine uptake of cells cultured without antigen}}$$

Vasovasostomy

This was undertaken using standard surgical methods without utilising microsurgical techniques (Jenkins and Blacklock, 1979). Following testicular biopsy the vasectomy sites were excised. End-to-end anastomosis using 3/0 Dexon with a monofilament nylon splint was performed. The splints were removed on the fifth post-operative day and the patient mobilised on the seventh post-operative day.

Testicular Biopsy

All specimens were fixed immediately in Bouin's solution and stained with haematoxylin and eosin (H and E) or phosphotungstic acid haematoxylin (PTAH).

Results

Lymphocyte Transformation

The *in vitro* response of leucocytes from patients up to 8 years after vasectomy cultured with heat-treated extract of human sperm (BHS) is shown in Figure 1. No leucocytes show an SR greater than 2.5 and this does not differ from the response to BHS prior to vasectomy reported in the previous study. There is no evidence, therefore, of an *in vitro* response to the sperm extract after vasectomy.

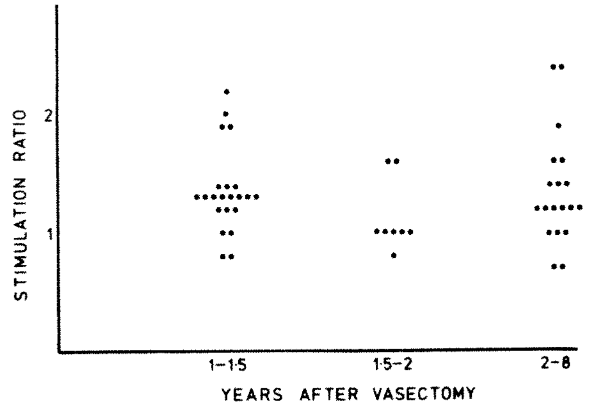

Fig. 1 Stimulation Ratio: leucocytes cultured with heat-treated human sperm.

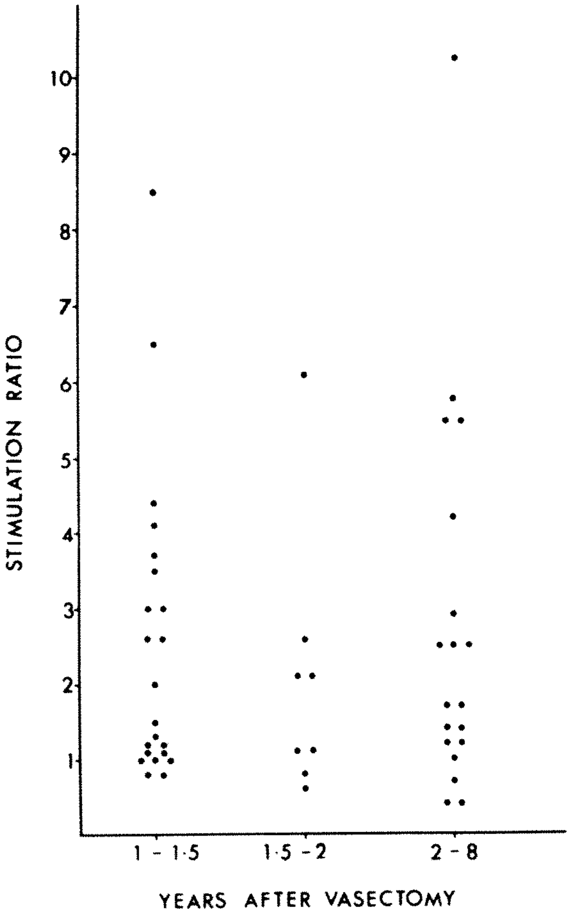

Fig. 2 Stimulation Ratio: leucocytes cultured with PPD.

However, the *in vitro* response of leucocytes from the same patients cultured with PPD is shown in Figure 2. Within each time-related group, cultured cells from several patients showed significant uptake of ^{3}H-thymidine ($SR > 2.0$). This provides a technical control.

Testicular Histology

The histological appearance of the testicular tissue taken from the 11 patients at the time of vasovasostomy, 2 to 10* years (average 42 months) after vasectomy, was abnormal in each case (Fig. 3).

All showed intertubular oedema and reduced spermatogenesis. The abnormalities were patchy with normal tubules adjacent to those with

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* Culture result invalid in this patient.

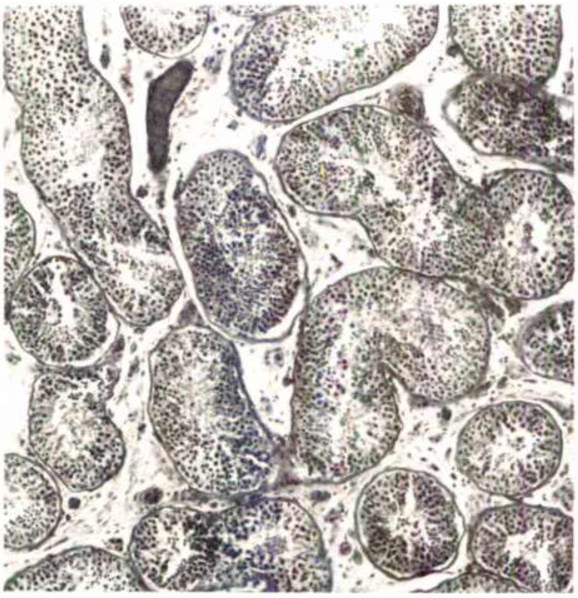

Fig. 3 Normal human testis: 20-year-old (H and E ×70).

maturation arrest (Fig. 4a). Vacuolisation of the tubular contents was occasionally seen (Fig. 4b). In some patients the absence of the more mature elements suggested a back-pressure atrophy. Some biopsies showed a disorganisation of spermatogenesis with hypertrophy of the spermatogonia and fewer mature spermatozoa (Fig. 5). Figure 5 also shows an intraluminal giant cell. The severity of the histological abnormality did not appear to be related to the duration of the vasectomy.

Subsequent Fertility

Of the 11 patients who underwent vasovasostomy, the wives of 7 (63.6%) conceived 5 to 24 months (average 11.3 months) after the anastomosis. Two patients have been lost to follow-up, although 1 was known to be euspermic 2 years after the reversal. The other 2 patients continue under review, 1 with oligozoospermia, the other being euspermic 3 years after operation.

The severity of the histological abnormality was not related to the subsequent fertility or the conception time.

Discussion

The conclusion of the previous *in vitro* study was that cell-mediated immunity to sperm did not develop within 1 year of vasectomy in man (Muir *et al.*, 1977). The present study suggests that cell-mediated immunity to sperm does not occur up to 8 years after vasectomy, and therefore presumably not at all.

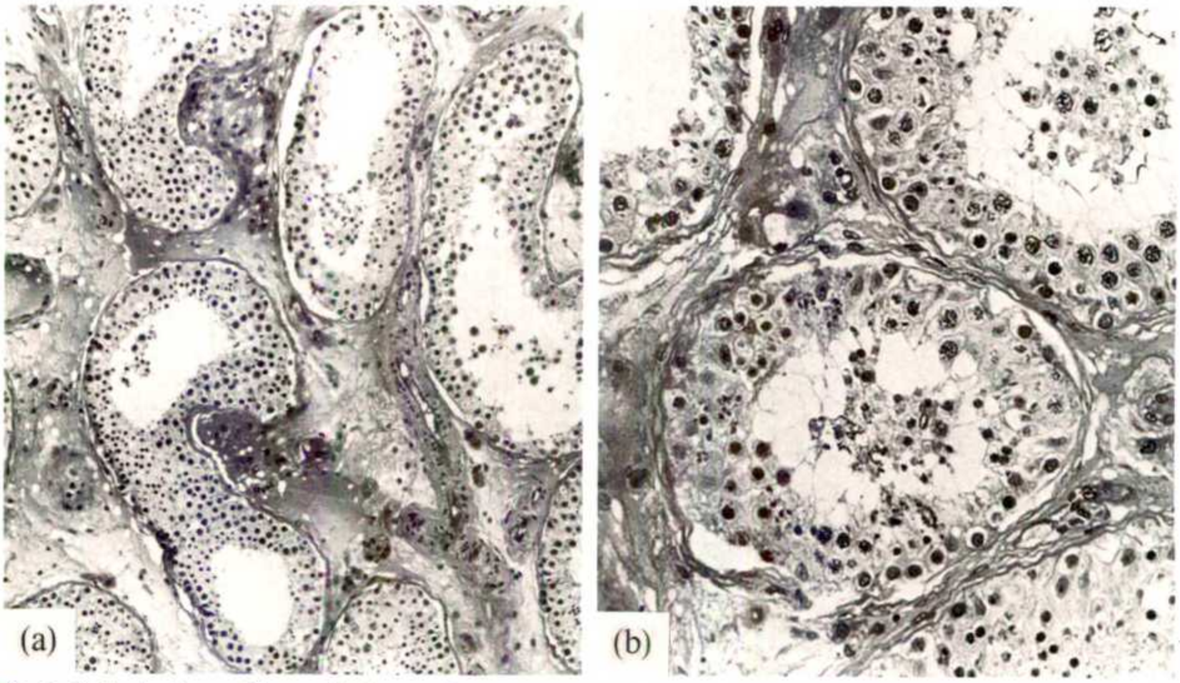

Fig. 4 Testicular biopsy: 30-year-old, 2 years after vasectomy, (a) (H and E ×16), (b) (H and E ×40).

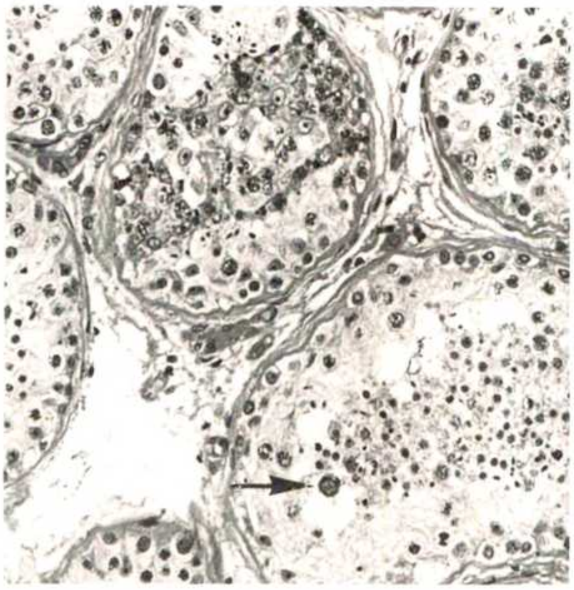

Fig. 5 Testicular biopsy: 35-year-old, 4 years after vasectomy (H and E ×40).

It is surprising that the testicular abnormalities noted had no apparent effect on subsequent fertility despite their severity. The visible changes may therefore be rapidly reversible after successful reanastomosis or be functionally insignificant.

It had been considered that cell-mediated immunity to sperm might be an aetiological factor in some cases of male infertility. Histological changes similar to those recognised following vasectomy have been reported in a series of testicular biopsies from cases being investigated for infertility (Meinhard *et al.*, 1973). However, the aetiology of the testicular abnormality seen after vasectomy remains unknown. It may be mechanical, hormonal, immunological or any combination of these or other factors.

Distension of the occluded vas with increased intraluminal pressure is known to occur following vasectomy (Silber, 1977) and may possibly cause a back-pressure atrophy. Such an effect could well account for a reduction in mature spermatozoa and be potentially reversible, but it is unlikely to cause the derangement of spermatogenesis.

The possibility of the testicular lesion being secondary to a hormonal imbalance has been investigated (Smith *et al.*, 1976; Kinson *et al.*, 1977). It was concluded, however, that apart from the immediate post-vasectomy period there was no evidence of hormonal abnormality.

It has been shown (Bigazzi *et al.*, 1976) that after vasectomy in the rabbit, testicular lesions can occur which might be caused by the deposition of immune-complexes. The lesions described were similar to those developing in the testes of the vasectomised guinea pig (Muir *et al.*, 1976).

It is suggested that the histological abnormalities in man reported in this study might be caused by a combination of sperm antibody deposition together with some degree of back-pressure atrophy.

After successful vasovasostomy the intraluminal tension will be reduced and sperm antibody levels might fall due to sperm excretion rather than accumulation. However, the evidence for conception within such a short time of operation suggests that a persisting immune response to sperm might not impair fertility.

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H. G. Hanley, CBE, MD, FRCS, FACS, formerly Dean of the Institute of Basic Medical Sciences. Now retired.

Requests for reprints to: Surgeon Lt. Cdr. I. L. Jenkins, RN, Department of Urology, Royal Naval Hospital, Haslar, Gosport PO12 2AA.

British Journal of Urology (1979), **51**, 411

Case Reports

Wilms' Tumour with Polycystic Kidney

This is the first report in the literature of a patient with a Wilms' tumour in a polycystic kidney.

Case Report

A 2-year-old male child was admitted with an abdominal swelling which had gradually increased in size over the preceding 6 months. The swelling extended from the left hypochondrium to the left iliac fossa and across the midline.

Intravenous pyelography revealed normal excretion of dye on the right side but no excretion on the left even after 1 h. The diagnosis of Wilms' tumour was made.

At operation a small, yellow nodule was found in the left lobe of the liver. Partial excision of the liver was therefore carried out together with a left total nephrectomy. The child died on the tenth post-operative day.

Gross Pathology. The kidney measured 20 × 15 × 10 cm and contained a mixture of solid and cystic areas. The cysts were well defined, filled with thin, yellow fluid and separated from each other by thin, fibrous septa. The solid areas had a variegated appearance, varying from yellow to brown with a few haemorrhagic zones. The liver nodule was small, well circumscribed, haemorrhagic and necrotic.

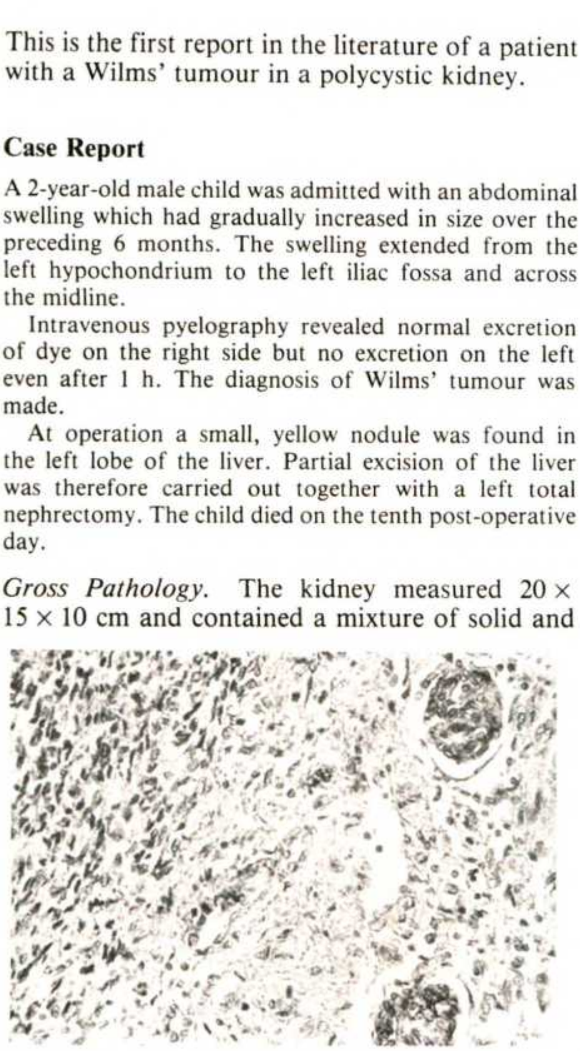

Fig. Poorly developed glomeruli and compressed tubules. Note tumour mass in upper corner (H and E ×80).

Microscopic Pathology. The renal parenchyma was replaced by Wilms' tumour. The cysts were lined by low cuboidal epithelium. The intercystic stroma was infiltrated by malignant cells. The liver nodule was metastatic Wilms' tumour (Fig.).

Comment

A critical review of the literature reveals only 18 cases in which polycystic kidney was associated with malignant tumour, and in none was the tumour a nephroblastoma (Howard and Young, 1969; Cole and Gill, 1973). The cysts were type II cysts (Osathanondh and Potter, 1964).

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The Authors

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British Journal of Urology (1979), **51**, 412

Sertoli Cell Tumour of the Testis

This tumour is thought to be derived from the testicular stroma and has also been called a gonadal stromal tumour and an androblastoma. It is rare and occurs in 1.2% of tumours referred to the Testicular Tumour Panel between 1958 and 1973 (Pugh, 1976).

Case Report

A 24-year-old presented with a painless swelling of the left testis of 2 years' duration. The testis measured 8 × 4.5 × 3.2 cm; the right testis was normal. He had no other signs or symptoms and his general investigations were negative. The left testis was explored and a frozen section suggested a "non-malignant growth". The testis was removed. The tumour measured 4.5 × 3.5 × 3.2 cm and had the microscopic appearance of a Sertoli cell tumour of the stromal type without evidence of malignancy (Fig.). The patient was discharged from hospital on the seventh post-operative day. Hormonal measurement after orchiectomy showed an increased output of 17 oxysteroids (25.7 units). Urinary gonadotrophins were not measured.

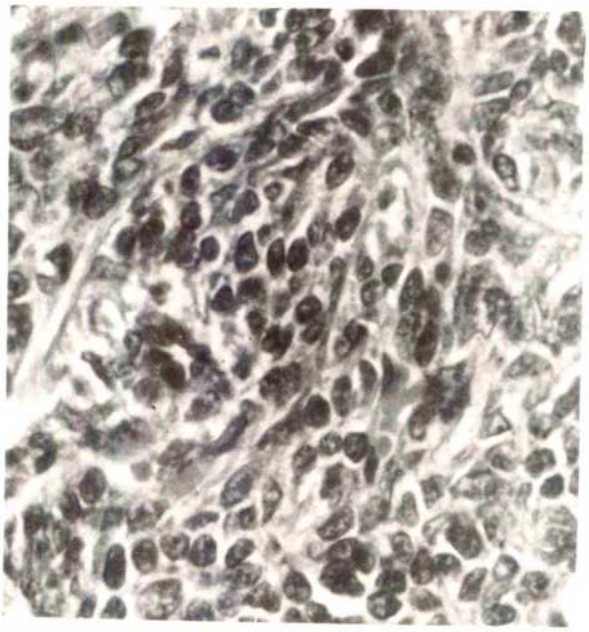
Fig. Photomicrograph of tumour (H and E ×450).

Comment

The first case of Sertoli cell tumour was recorded in 1944 (Teilum, 1958) but there are now more than 70 reports in the literature (Kalis and Goulandris, 1974). The patient usually complains of a small, hard, rapidly growing swelling of the testis which may be associated with an undescended testis, or with other tumours. Approximately one-third present with some degree of gynaecomastia which resolves after orchiectomy.

The tumour in this case was characteristically discrete from the testis and off-white in colour. Microscopically there are 3 types, depending upon the proportion of epithelial and stromal tissue. The stromal type is the most undifferentiated; the epithelial or tubular type is more differentiated and associated with the production of female hormones; the third type is a mixture of both cell types.

Until 1966 there had been no report of a malignant Sertoli cell tumour but 14 cases progressing to malignancy have now been reported (Pugh, 1976); the incidence of malignancy is probably between 10 and 20% and all cases require regular follow-up.

References

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British Journal of Urology (1979), **51**, 413

Dystrophic Calcifying Nodule with Osteoid Metaplasia of the Testis

Case Report

In December 1976 this 40-year-old male underwent a left orchiectomy for seminoma. This was followed by a course of radiotherapy but a plain X-ray of the abdomen had then shown an abnormal shadow in the region of the right testis. Physical examination revealed a tumour the size of the tip of the little finger in the right testis. The tumour was removed with preservation of the testicle; the tumour measured 18 × 12 × 11 mm and weighed 2 g. The histological diagnosis was a dystrophic calcified nodule with osteoid metaplasia (Fig.).

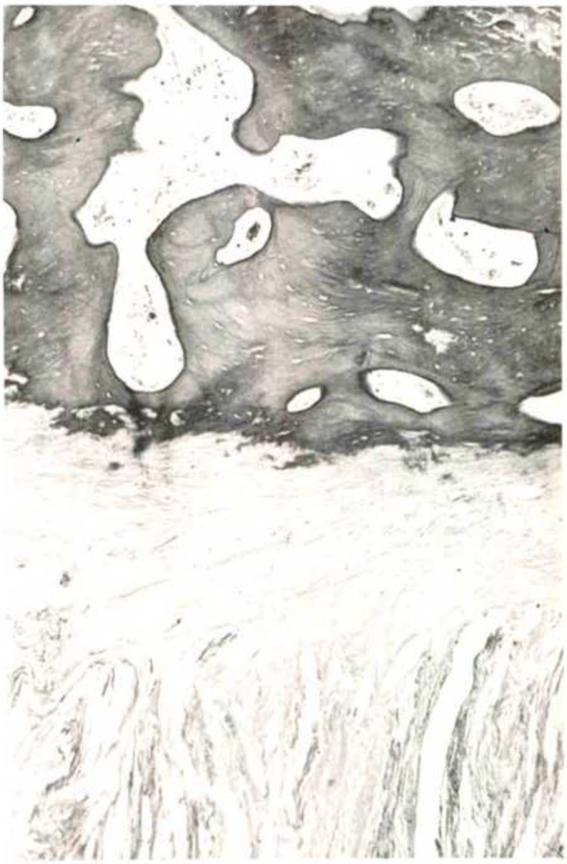

Fig. Photomicrograph of tumour (×40).

Comment

Ossifying interstitial cell tumour of the testis was reported by Minkowitz *et al.* in 1965. Ectopic ossification has been described in such diverse locations as the pelvis of the kidney, the wall of the artery, the eyes, muscles and tendon. From these observations it may be inferred that many types of connective tissue possess a latent osteogenic potency which is exhibited only rarely.

Reference

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British Journal of Urology (1979), **51**, 414

Renal Schistosomiasis

Case Report

This male patient, aged 52 years, had a past history of urinary schistosomiasis treated twice in childhood. In 1965 he was operated upon for a stricture of the left ureter and a stone in the right ureter. In June 1977 he was investigated for recent and persistent left renal pain. Investigation revealed a non-functioning left kidney and a functioning right kidney. The left kidney and ureter were removed. The enlarged left kidney revealed hard areas in the cortex with very dense perirenal adhesions and its pelvis and ureter were dilated and tortuous. The cut surface of the kidney revealed areas of yellow necrosis in the cortex and soft, friable tissue lining the pelvis. Microscopic examination showed areas of necrosis and dense fibrosis in the renal parenchyma around groups of calcified ova (Fig.) and the renal pelvis was infiltrated by a poorly differentiated transitional cell carcinoma.

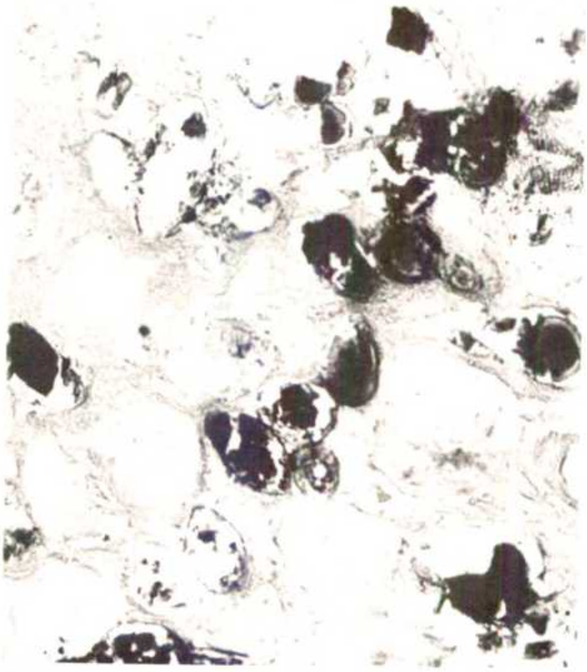

Fig. Section of the renal cortex showing a few glomeruli and calcified ova surrounded by dense fibrosis (× 150).

Comment

Despite the rarity of renal schistosomal lesions. Ruffer (1910) discovered schistosomal ova in the kidneys of 2 mummies of the twentieth dynasty. To our knowledge this is the first Case Report of schistosomal infiltration of the renal cortex. The infection possibly spread through adventitious anastomoses between the mesenteric vein and the veins of the renal cortex through pararenal and perirenal fat. The association with pelvic transitional cell carcinoma is interesting but probably incidental.

Reference

Ruffer, M. A. (1910). Note on the presence of "Bilharzia haematobia" in Egyptian mummies of the twentieth dynasty (1250-1000 BC). *British Medical Journal*, **1**, 16.

The Author

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British Journal of Urology (1979), **51**, 415

Perineal Calculus Formation with Kaufman's Prosthesis

Case Report

In 1972 the patient, a young male, had difficulty in passing urine after a benign spinal tumour was removed and the prostate resected. A second resection was required 6 months later and resulted in urinary incontinence. In November 1975 a Kaufman's prosthesis was implanted over the bulbous urethra. The patient became continent but one month after operation the wound became infected and a perineal fistula developed. It closed spontaneously with antibiotic treatment but the patient became incontinent again and had to wear a pubic pressure urinal. During the next 2 years he felt as if the prosthesis was growing and it became more mobile and uncomfortable.

In July 1977 the perineum was explored and a smooth, ovoid, calcium oxalate stone 6×4.5 cm was found in a large urethral diverticulum. Both stone and diverticulum were removed and the urethra was reconstructed around a catheter.

He recovered satisfactorily and was discharged home with sterile urine and a pubic pressure urinal.

The silicone gel of the prosthesis was found in the centre of the stone (Fig.).

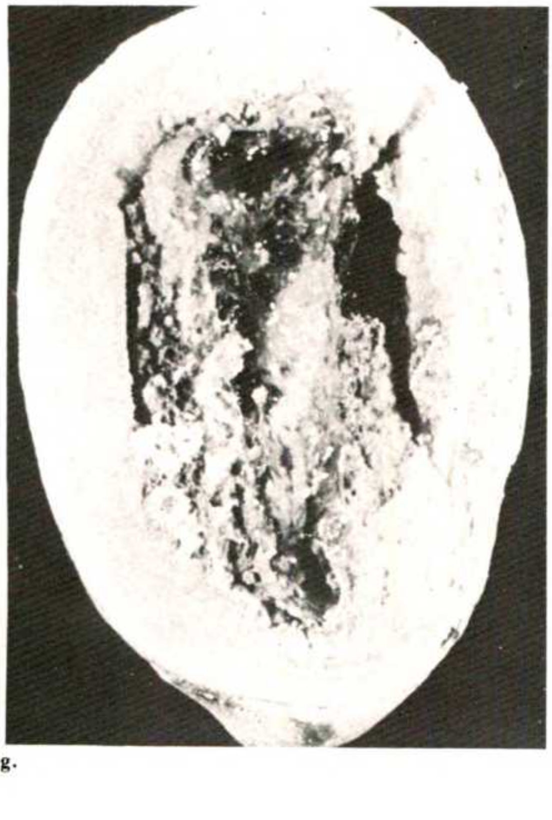

Fig.

Comment

The silicone gel prosthesis of Kaufman (1973) is implanted over the bulbous urethra in the perineum and aims at achieving continence by passive urethral resistance. The earlier model of velour dome prosthesis used in this patient tended to erode the urethra (Kaufman and Richie, 1973). With the unveloured dome prosthesis (Das and Kaufman, 1977) urethral erosion has been uncommon.

References

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Kaufman, J. J. and Richie, J. P. (1973). Urethral erosion: complications of Kaufman's anti-incontinence operation. *Urology*, **3**, 218.

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British Journal of Urology (1979), **51**, 416

A Metastatic Melanoma in the Spermatic Cord

In the current literature on paratesticular tumours, primary malignant tumours of the spermatic cord are relatively frequent, whereas only 17 cases of metastatic tumour have so far been described. They mostly refer to metastases from gastric, colonic, pancreatic, parathyroid and renal carcinoma (Del Gaudio *et al.*, 1964; Tabayashi and Tsuchiya, 1970).

Case Report

A 50-year-old male was admitted to hospital with a painless, slowly growing, walnut-sized swelling of 1 month's duration. Four years before this admission an excision of a left axillary cutaneous naevus had been performed. The swelling was located in the central part of the right inguinal canal. It had an irregular surface, was hard and could be moved freely. The right testis was normal. There were no urinary symptoms. The patient was healthy and had no fever. Blood chemistry was within normal limits except for an increased sedimentation rate. Chest radiography showed several metastatic shadows, especially in the left lung. IVP was normal. Inguinal incision revealed a hard mass (3 × 3.5 cm) attached to the spermatic cord. A right orchiectomy with ligation and division of the spermatic cord at the internal inguinal ring was performed (Fig.). Histological examination revealed melanosarcoma.

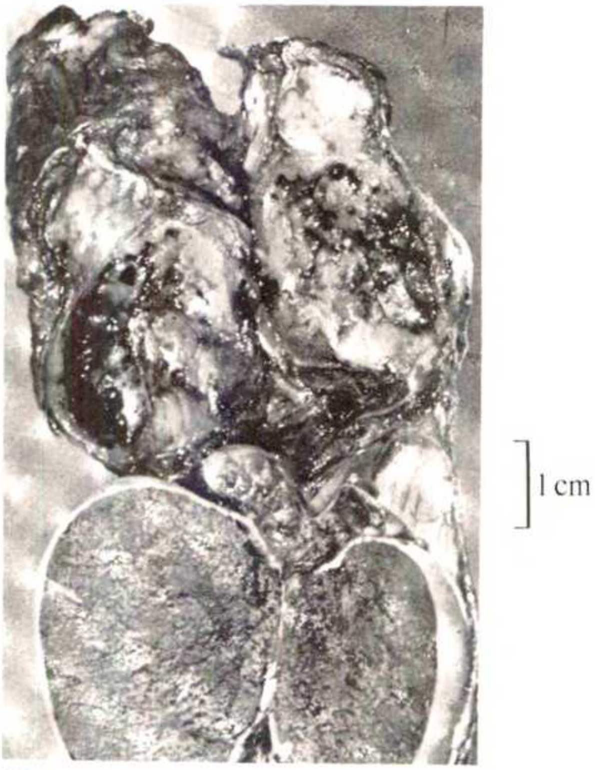

Fig.

Comment

This case is interesting because: (1) metastatic spermatic cord tumours are very rare; (2) the histological type of the tumour is very uncommon; (3) metastases were found as late as 4 years after resection of the primary tumour; and (4) such a case has not previously been reported. In secondary malignant tumours of the spermatic cord the presence of widespread metastases limits the treatment to total orchiectomy, as in our case, and chemotherapy.

References

Del Gaudio, A., Martelli, A. and Torchi, B. (1964). I tumori del funicolo spermatico. *Il Cancro*, **17**, 106-179.

Tabayashi, Y. and Tsuchiya, A. (1970). Metastatic tumor of the spermatic cord: case report. *Japanese Journal Clinical Urological*, **24**, 631-638.

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British Journal of Urology (1979), **51**, 417

Conferences and Courses

Ninth Meeting of the International Study Group for Steroid Hormones

Rome, Italy. 5-7 December 1979.

Further information from: Professor C. Conti, Clinica Medica V, Policlinico Umberto 1, Universita di Roma, 00100 Rome, Italy.

33rd Annual General Meeting of the Urological Society of Australasia

Christchurch, New Zealand. 24-28 February 1980.

Further particulars from: Mr Peter Maher, 10 Wybalena Road, Hunter's Hill, New South Wales 2110, Australia.

Canadian Urological Association: 1980 Annual Meeting

Banff, Alberta. 21-27 June 1980.

Further particulars from: Dr James O. Metcalfe, 421 Medical Arts Building, 11010 Jasper Avenue, Edmonton, Alberta, Canada T5K OK9.

International Symposium

Vienna, Austria. 23 and 24 November 1979.

The following topics will be discussed: latest treatment of urethral stricture in the male; indications, technique, post-operative care and late results with staghorn calculi.

Further particulars from: Dr P. Porpaczy, c/o Vienna Medical Academy, Alser Strasse 4, A-1090 Vienna, Austria.

Organisers wishing to have details of their courses and conferences published in the Journal should send details to J. E. Newsam, Western General Hospital, Edinburgh EH4 2XU.

Combined Meeting of BAUS and the Canadian Urological Association

Montreal, Canada. 21-25 June 1981.

In order to make provisional plans about transport and a short pre-congress tour, it is essential to have some idea of the number of British members likely to attend this meeting.

Any members of BAUS who are interested in attending should communicate with Mr J. L. Williams, Honorary Secretary, BAUS, Royal College of Surgeons, Lincoln's Inn Fields, London WC2, as soon as possible.

Book Reviews

Nephrolithiasis: Pathogenesis and Treatment. Fredric Lawrence Coe. Pp. xx + 235. London: Year Book Medical Publishers Ltd. 1978. Price £21.25.

This book is relevant to all urologists. It is written by a distinguished stone expert who lucidly explains modern thinking about stone pathogenesis and treatment. Rightly, most of the book is devoted to the common stone types. All of the articles are intelligible to the surgeon, although the surgical aspects of stone disease are not covered. I can recommend this book as being a useful addition to the library of every urology department.

Reflux and Renal Scarring. P. G. Ransley and R. A. Risdon. British Journal of Radiology Supplement 14. Pp. v + 35, illustrated. London: British Journal of Radiology, 1978. Price £3.60 (members of the British Institute of Radiology £3.00).

In this lucid account of their experiments on the pathogenesis of reflux nephropathy the authors add important new observations on the relationship between reflux, infection and pyelonephritic scarring. The study was carried out on pigs and builds upon the authors' previous work and that of Hodson.

The investigations are clearly described and well illustrated and the results emphasise the importance of infection and reflux together in the production of renal parenchymal scarring. This is an important contribution to the understanding of the problem. The authors' discussion of their findings and the clinical significance of these results will be of interest to all those concerned with the management of urinary infection in childhood.

Encyclopedia of Urology, V/I Supplement. Diagnostic Radiology. L. Andersson, I. Fernström, G. R. Leopold, J. U. Schlegel and L. B. Talner. Pp. 199, 88 figs. Berlin: Springer-Verlag, 1977. Price DM 98, US $45.10.

This supplement to the volume on Diagnostic Radiology, published in 1962, gives an excellent account of 2 important techniques in urological radiology which have become established since that time. The use of radio-isotopes for studies of function and, to a lesser extent, structure in urinary tract disease is well described and illustrated. The section on urological ultrasound is from another centre in the USA and is an extremely lucid account of the technique and its present position in urological diagnosis. The final section describes percutaneous puncture nephrostomy and the authors from Stockholm give a detailed description of this radiological technique in the management of ureteric obstruction.

This is an authoritative, well illustrated, and easily read little book. The sections on radio-isotopes and ultrasound particularly are recommended to urologists who are becoming involved with these diagnostic techniques.

Transplantation Antigens—A Study in Serological Data Analysis. N. Selwood and A. Hedges. Pp. xviii + 147. Chichester: J. Wiley, 1978. Price £9.50.

An intriguing book that discusses the development of an approach, based on numerical taxonomy, to the analysis of data from serological reactions. The principal of the method is based on the mutual resemblance of objects observed over as large a *number* of characteristics as possible, with equal emphasis placed on each characteristic. The claimed advantages of the method when compared with established statistical treatments are simplicity and versatility. The method makes few of the complex assumptions concerning sampling and distribution on which the statistical methods are dependent.

The starting point for both the statistical and numerical methods can be the same 2 × 2 table. The numerical method by generation of a compound coefficient and with a knowledge of reaction frequency acts as a summary of 2 × 2 table data and can be used directly for preparation of serographs.

It is unfortunate that the book itself is written in a "confusing" style and in many instances it excels in stating the obvious in a confusing manner, although there are occasionally bursts of lucidity, *e.g.* Chapter 1. The average serologist will need to read this book several times before a true appreciation is gained.

The book can be thoroughly recommended as a thought-provoking exercise and even if it serves only to show the limitation of current serological data analysis, it will have served its purpose. Perhaps the statement on page 59 serves best to put the book in perspective: "Whether it is necessary to use anything other than the 2 × 2 table is, in general, a purely practical consideration".

1978 Year Book of Urology. Edited by John T. Grayhack. Pp. 381. London: Year Book Medical Publishers. 1978. Price £18.50.

This Year Book Series in Urology continues its high standard. Dr Grayhack suggests that this volume should be dedicated to the urological oncologist, but in fact the volume is as comprehensive as ever and the editorial comments as sharp as ever. Although a urologist in training will have covered much of the contents in journals and at meetings, it is still an excellent revision course for all urologists.

Books Received

Practical Diagnosis. Renal Disease. M. A. Kirschenbaum. Pp. 253. Boston: Houghton Mifflin Company. 1978.

Advances in Nephrology. Edited by J. Hamburger. Volume 8. London: Year Book Medical Publishers. 1979. Price £36.75.

Understanding Your New Life with Dialysis. Edith T. Oberley and Terry D. Oberley. Second edition. Pp. 146. Springfield, Illinois: C. C. Thomas. 1979.

Dialysis Transplantation Nephrology. Proceedings of the European Dialysis and Transplant Association. Edited by H. B. Robinson and J. B. Hawkins. Volume 15. Pp. 662. Tunbridge Wells: Pitman Medical Publishing Co. 1979. £20.00.

British Journal of Urology (1979), 51, 419-426

Abstracts of the Proceedings of the Urological Society of Australasia 32nd Annual General Meeting, Melbourne, Australia, 1979

President: I. N. Nunn (Melbourne)
Honorary Secretary: P. O. Maher (Sydney)
Editor: J. P. Maddern (Adelaide)

Bladder Instability: Urology's Largest Problem

By J. C. Smith

Department of Urology and Nuffield Institute of Medical Research, Oxford, England

More extensive use of the cystometrogram has confirmed that the phenonomen of bladder instability is responsible for most cases of urgency and urge incontinence of urine. Over the past 7 years the development in Oxford of the technique of prolonged bladder distension under epidural anaesthesia has proved an effective way of controlling the symptoms and of producing objective change in the cystometrogram.

The major complication has been bladder rupture which occurred in about 5% of those patients for whom prolonged bladder distension was performed for instability. Bladder rupture was confirmed by cystometrogram and treated by catheter drainage and antibiotics. Surgical exploration was not necessary for this complication in any case.

Results in those patients who sustained bladder rupture compare favourably with those in whom no rupture occurred.

The Hydrodynamics of Obstruction

By F. Brantley Scott

Baylor College of Medicine and St Luke's Episcopal Hospital, Houston, Texas, USA

In basic hydrodynamic terms the flow rate along a tube is a product of the velocity by area. Since the velocity of the urinary stream depends upon pressure, an increase in pressure will increase flow, but also an increase in area of the conduit will increase flow. Increasing the area is far more effective in improving flow than by increasing pressure. For example, a 50% increase in the diameter of a circular meatus results in a 100% increase in flow with a constant pressure, but with a constant diameter a 500% increase in pressure is required to bring about a 100% increase in flow. This becomes more significant with the realisation that the detrusor is usually incapable of producing more than a 50% increase in pressure in response to obstruction.

Flow Study Evaluation of Urethral Obstruction

By I. N. Nunn

Royal Melbourne Hospital, Melbourne, Victoria

The use of the mictiograph as an objective measurement in the assessment of urethral obstruction was discussed.

In addition to a maximum voiding rate an assessment of the whole curve, including the rate of rise and fall, the time taken to reach a maximum voiding time, curve shape and voided volume, is most important.

Fifty consecutive patients with and without obstruction were reviewed. Twenty-five had pre-treatment and post-treatment curves; 16 had treatment deferred and in 9 no post-operative curves were possible.

Of the 23 treated for obstruction, 21 had a slow rise greater than 5 s, 23 had a slow variable fall and excessive bulbocavernosus squirts. All had a maximum flow rate of less than 15 ml/s (average 5 ml/s) and 22 had a voiding time greater than 30 s (average 79 s).

In the post-operative curves those with a good clinical result (21) had a flow rate greater than 15 ml/s (average 21), 2 had poor results and because of a urethral stricture the other still had symptoms although the curve had reverted to normal.

In all but 3 patients the voiding time reverted to less than 30 s (average 20 s).

Assuming an adequate voided volume (greater than 100 ml), a flow rate of less than 15 ml/s is indicative of obstruction and a voiding time of more than 30 s is abnormal.

This simple non-invasive test can be most helpful in deciding on management in the difficult borderline case.

An Experimental Comparison Between the Actions of Propantheline and Imipramine

By A. G. S. Tulloch and K. E. Creed

Sir Charles Gairdner Hospital, Perth, Western Australia

Adult female dogs were used as the experimental model, The pelvic nerve was stimulated electrically while the rise in bladder pressure was recorded by a catheter in the bladder. The submandibular duct was cannulated and the chorda tympani was stimulated electrically where the fibres ran with the lingual nerve. The number of drops of saliva was recorded, while the chorda tympani was stimulated supramaximally for 10 s. Propantheline was given intravenously in increasing doses from one microgram to 300 micrograms per kilogram of body weight. After each injection of propantheline the pelvic and chorda tympani nerves were stimulated electrically for 10 s and the rise of bladder pressure and number of drops of saliva produced were recorded. On different dogs imipramine was given in doses varying from 1 to 3000 micrograms per kg. Following electrical stimulation the rise of bladder pressure and the amount of saliva secreted were recorded.

Propantheline almost completely blocked the salivary gland secretion when given at 10 micrograms per kg but produced only a 25% reduction of the intravesical pressure rise with pelvic nerve stimulation. At low doses of imipramine—up to 100 micrograms per kg—there was little change in the salivary production but a 15% fall in intravesical pressure rise. With increasing doses of imipramine there was a marked reduction in intravesical pressure response to pelvic nerve stimulation with very little further fall in salivary gland secretion.

The experimental data suggest that the action of imipramine is not anticholinergic and that imipramine is the more promising drug to use in bladder instability. Possibly better clinical results might be obtained if both drugs were used simultaneously as the pharmacological action of each drug seems different.

Testicular Vein Venography in the Infertile Male

By G. Reisner and K. W. Bell

St Francis Xavier Calrini Hospital, Melbourne, Victoria

Patients in this study were the male partners of an infertile couple. They had either a low sperm count or low sperm motility. Patients with a clinically detectable varicocele were excluded, as were other patients with an obvious cause of male infertility. The aim of the study was to determine the incidence of reflux from the left renal vein into the left pampiniform plexus.

Forty-five patients were studied by left testicular or left renal vein catheterisation. Twenty-five patients had venous reflux demonstrated radiologically. One study was unsatisfactory because of abnormal venous anatomy. Nineteen patients had functioning valves in the left testicular vein(s) which prevented reflux. Collateral circulation between both sides of the scrotum was demonstrated in 2 instances. Communication between pelvic veins and the pampiniform plexus was observed in one case.

Of the twenty-five patients with venous reflux, 14 were subjected to high ligation of the left testicular vein(s). Follow-up of 3 months or more was available in 10 patients. In this group, 5 patients had improved either sperm count or motility or both. In 3 patients semen quality deteriorated, and in 2 cases no semen was obtainable in follow-up.

Two pregnancies were noted. Significant tubal or ovarian factors were noted in 9 of 14 wives of the patients who had undergone surgery.

In this study we sought to determine the presence of venous reflux which is not to be equated to the presence of a clinical varicocele. The results of surgery in patients with reflux are encouraging thus far and it may be that the results will be equivalent to those obtained after ligation of clinical varicocele.

In addition, it would seem that venography is a valuable method of confirming the clinical suspicion of a varicocele. It has the additional advantage of defining the venous anatomy for the surgeon, thus hopefully reducing the incidence of persistent post-operative varicocele or operative damage to the testicular artery.

A Cost Analysis Study of the Management of Lower Ureteric Calculi

By R. B. Brown

Alfred Hospital, Melbourne, Victoria

Two hundred and sixteen non-consecutive patients presenting with low ureteric calculi measuring between 0.1 and 0.7 cm were assessed to determine the natural history and complications of spontaneous expulsion, the results and complications of attempted endoscopic extraction, and the financial costs to the community of the different methods of management.

The survey was restricted to those patients with a solitary low ureteric calculus and an otherwise normal, although obstructed, system.

The average age was 46 years. The right ureter was involved in 117 and the left in 99 cases. Males presented 2.3 times more commonly than females.

Of the 100 patients with stones measuring 0.5 cm or less, followed for up to 12 months, the majority passed their stones spontaneously, without any detectable complications, within 3 months of presentation. However, of 16 patients with calculi measuring between 0.6 and 0.7 cm, also followed for up to 12 months, only 7 passed their calculus.

Of the 100 attempted endoscopic calculus extractions the operative success rate averaged 62% for those calculi measuring 0.5 cm or less but only 22% for calculi measuring 0.6 to 0.7 cm. The only 2 complications in the series came from the attempted extraction of large calculi.

The financial costs to the community of non-surgical management, successful endoscopic extraction, failed endoscopic extraction and subsequent spontaneous passage or open ureterolithotomy, were detailed. Spontaneous non-hospital expulsion provided the lowest cost, while failed endoscopic extraction of the larger calculus provided the highest cost.

These results and costs suggest that hospitalisation is best avoided in the case of smaller calculi, whilst larger calculi are best treated by immediate open ureterolithotomy.

Non-Seminomatous Testicular Tumours: Justification for an Aggressive Regime

By G. Hirst
Brisbane, Queensland

For the purpose of treatment, non-seminomatous testicular tumours are considered as early or advanced disease, early being Stage I and Stage II (non-bulky) and advanced Stage II (bulky) and Stage III.

In early stage disease, management is based on the total ablation of all involved retroperitoneal lymph nodes. This is best achieved by bilateral retroperitoneal lymph node dissection. However, a comparison of the results of surgery and radiotherapy showed no statistically significant difference between the 2 modalities, with 80% of patients being cured by either.

In advanced disease Einhorn, using a combination of Platinum, Bleomycin and Vinblastine, has reported the best results with 60% of patients having no evidence of disease at 2 years. A preliminary report of 43 patients from 3 Australian centres using an Einhorn-type regime shows a 77% complete remission rate and 56% of patients with no evidence of disease at 3 to 14 months. The overall drug-related death rate was 14%, although only 7% for the 29 patients who had no non-surgical treatment prior to chemotherapy. Fourteen patients previously treated by radiotherapy or other chemotherapeutic regimes had a 35% drug-related death rate.

Twenty per cent of patients treated for early stage disease will relapse and require chemotherapy. In order to minimise the drug-related death rate in this relapsing group, radiotherapy should not be used in early stage disease. The results also suggest that there is no place for adjuvant or sub-optimal chemotherapy.

Testicular Injury—Diagnosis and Management

By John S. Jose
Royal Adelaide Hospital, Adelaide, South Australia

Rupture of the testis is an uncommon occurrence, but is probably more common than recognised because of inaccurate diagnosis. The mobility of the testis within the scrotum and the strength of the tunica albuginea tend to protect it from rupture, but injury will occur if sufficient force presses the testis against the pubic bones.

Testicular injury may follow sporting and road accidents, direct blows and kicks and falls astride. Three types of injury may occur.

1. Rupture of the testis, with which is always associated a traumatic haematoma. The common lesion is a transverse rupture of the body of the testis, sparing the epididymis, and through this parenchyma is extruded.

   Surgical repair is frequently possible with conservation of the testis and its spermatogenic function, although following a gross injury and delayed surgical exploration (greater than 3 days after injury) orchiectomy is more likely.
2. Haematoma of the testis. A subcapsular or parenchymal haematoma forms beneath the intact tunica albuginea which may lead to pressure necrosis or testicular atrophy. Haematoma of the testis is not associated with significant haematocele, the testis remaining palpable and discrete, hard and acutely tender. At exploration it appears swollen, tense and blue in colour. Operative decompression will preserve function. Minor contusions of the testis, however, resolve without surgical intervention.
3. Traumatic haematocele is most commonly associated with an underlying rupture. The diagnosis of rupture cannot be made absolutely without surgical exploration, although ultrasound examination of an injured testis can demonstrate a concealed rupture, confirming the need for intervention.

Early operative exploration in all cases of major testicular injury and traumatic haematocele is recommended.

Transurethral Resection—Water and Safety

By David Gunter
Alfred Hospital, Melbourne, Victoria

In a personal series of 1022 consecutive unselected prostatectomies, including all retentions, the mortality was 0.4%. A transurethral resection was used in 944 cases and a retropubic operation in 78 cases. There was no mortality in the open cases but a 0.54% mortality in the transurethral resection groups. No patient who died suffered from oliguria or septicaemia.

In an attempt to assess the safety of water as an irrigating fluid 136 transurethral resections were subject to a prospective study. The age of the patients ranged from 50 to 92 (average 66.4), while the weight of gland resected varied from 10 to 150 g (average 48.6 g); 10.7% of the resected glands were malignant.

In an attempt to minimise the volume of water entering the bloodstream, a stand holding the reservoir of irrigating fluid was attached to the table. The base of the reservoir was invariably 20 cm or less above the symphysis pubis. A drip chamber was incorporated in the tubing and constantly observed by the scrub nurse, who notified the surgeon if the water flow faltered, and the bladder was emptied immediately. An intravenous infusion of sodium chloride 3% 300 ml was given in all cases and a further 200 ml if the operation took longer than 60 min. Intravenous frusemide 10 to 20 mg was given at the end of operation in most cases.

Post-operatively, if urine output was less than 100 ml/h in any 2-h period, intravenous frusemide 10 mg was administered.

Urea, electrolytes and serum bilirubin were estimated pre-operatively, at the end of operation and on the first day post-operatively. At the end of operation the serum urea had risen by more than 3 mmol/l in 2.3%. On the day after operation the serum urea had risen by more than 3 mmol/l in 3%. The 2 highest estimations noted post-operatively a day later were 15.5 mmol/l and 24.6 mmol/l. However, the pre-operative levels were 10.8 mmol/l and 15.5 mmol/l respectively, serum electrolytes showed no significant change. The serum bilirubin pre-operatively averaged 15 mmol/l, at the end of the operation averaged 17.3 mmol/l, and 24 h later averaged 16.4 mmol/l. In no cases were any serious sequelae encountered from these changes. It is considered that water is a safe irrigating agent provided that the pressure used during resection is kept constant and below 20 cm, no undue bladder pressure is allowed to develop and an adequate diuresis is established post-operatively.

A Staged Incision for the "Difficult Kidney"

By Bruce S. Pearson
Royal Prince Alfred Hospital, Sydney, New South Wales

The use of a staged incision allows excellent exposure of the kidney which is expected to present operative difficulty, *e.g.* carcinoma of the kidney or when difficulties are encountered during renal operations.

Stage I: is to excise the eleventh rib.
Stage II: is the forward and upward extension of the incision around the costal margin and towards the xiphisternum. This increases the access in the region of the renal pedicle and is preferable to extending the incision downwards away from the pedicle in the usual incision.
Stage III: is the backward and upward extension, excising a 3 cm length of the tenth rib. The diaphragm and pleura are freed and pushed upwards. This produces a "U"-shaped incision, increasing the access without entering the pleural cavity. An eleventh rib incision provides about 120 mm of transverse exposure. This "U" flap produces 220 mm exposure together with better exposure at the 2 ends of the incision.
Stage IV: the pleura and diaphragm may be incised to produce a thoraco-abdominal incision with wider exposure than the usual linear thoraco-abdominal incision. If Stage IV is not needed, post-operative morbidity is reduced by remaining extrapleural.

Post-operative progress and morbidity do not differ from the classical renal incisions.

Sir Douglas Shields' Vice-Regal Ureterolithotomy and its Sequelae

By Leonard J. T. Murphy
Melbourne, Victoria

The distinguished career of Sir Douglas Shields deserves mention at a urological meeting, not because he was a urologist, but because the cornerstone of his career was the remarkable operation of ureterolithotomy performed by him in 1910 upon the Countess of Dudley.

Shields graduated in 1898 and, after serving briefly in the South African War, he commenced practice in Seymour, 60 miles from Melbourne, where he built up a reputation as a surgeon. In 1905 he was appointed to the surgical staff of St Vincent's Hospital, where he became senior surgeon in 1908 and in the same year he was appointed consultant surgeon to the Governor-General.

In 1910 the Countess of Dudley, the Governor-General's Lady, required a ureterolithotomy, a recent operation for ureteric calculus by Hurry Fenwick of London having failed to relieve her symptoms. With the help of Hugh Devine and Thomas Dunhill, Shields successfully carried out a transperitoneal operation to remove the stone from under the broad ligament.

Two years later, on the advice of the grateful Countess, who thought his talents were wasted in Australia, he went to London and with the help of a gift of £30,000 he built his own hospital in Park Lane. He developed a very successful practice among the aristocracy and landed gentry, largely due to the influence of the Countess. His war service gained him a knighthood and other honours. Amongst his distinguished patients were Queen Mary and Sir Donald Bradman. The remarkable career of this former Victorian country practitioner ended in 1952.

Occupational Aspects of Bladder Cancer

By G. Gibson
Sydney Hospital, Sydney, New South Wales

A man of 58 years had haematuria whilst on holiday in England. He was found to have a bladder tumour and underwent total cystectomy and ileal loop urinary diversion. As he gave a history of exposure to dyestuffs in the course of 16 years' employment in the textile industry, he was referred for the opinion of a urologist as to the relevance of his former occupation in the cause of the bladder tumour.

After Rehn recognised the first cases of bladder cancer of industrial origin in the German dyestuff industry in 1895, the principal carcinogenic agents were identified as Benzidine, 4 Amido-Di-Phenyl, and 1 and 2 Naphthylamine, all aromatic amines derived from coal tar. Case found an increased risk in dyestuff manufacturing workers, which extended to users of the products in the rubber industry. Since then, other users of dyestuffs, including textile workers, have been identified as being exposed to carcinogenic amines. Although the manufacture of the carcinogenic amines was discontinued in England in 1950, 1 Naphthylamine and Benzidine have been used in textile printing, and related compounds, which are carcinogenic in animals, are used as intermediates in dye manufacture.

It was not possible to establish that any of the dyes or chemicals used by the patient were known carcinogens, and therefore it cannot be established with certainty that his bladder tumour was due to his occupation. Nevertheless, there is circumstantial evidence of carcinogeneity of related substances in animals.

Update on the AMS Inflatable Sphincter

By F. Brantley Scott

Baylor College of Medicine and St Luke's Episcopal Hospital, Houston, Texas, USA

Ideally on artificial sphincter should cause no periurethral fibrosis or pressure necrosis. It should have its occlusive pressure automatically controlled by the device itself and prevent stress incontinence. While being suitable for both male and female patients it should not interfere with sexual function and require minimal surgery and yet allow the release of a bladder pressure that is unphysiological. Voiding must be free and unobstructive and continence restored to a high percentage of patients, while at the same time catheterisation must present no difficulties.

Experience with the AMS inflatable sphincter models 721, 742 and 742 B and C was reviewed. The artificial sphincter AMS 742 B and C appear most suitable in satisfying all of the above requirements.

Implantation of a Penile Prosthesis in the Treatment of Impotence

By F. Brantley Scott,

Baylor College of Medicine and St Luke's Episcopal Hospital, Houston, Texas, USA

Three hundred and two patients with erectile impotence received implantation of an inflatable penile prosthesis between February 1973 and December 1978. Causes of the impotence included diabetes mellitus, peripheral vascular disease, radical surgery, trauma, Peyronie's disease and psychogenic factors.

The inflatable penile prosthesis, which can be implanted through an incision in the median raphe at the penoscrotal angle, has the advantages of providing flaccidity as well as rigidity, a normal or greater than normal rigidity with a normal or greater than normal girth. Subsequent cystoscopic procedures are not prevented and normal micturition occurs without post-operative urinary retention. Pressure necrosis was not encountered and the prothesis resulted in sexual satisfaction to both partners in over 95% of cases.

Nocturnal Penile Tumescence (N.P.T.) Monitoring in Penile Surgery

By Donald Moss

St John of God Hospital, Ballarat, Victoria

All potent males have a number of penile erections during each night's sleep, in the absence of sleep disturbance or drug effects. These nocturnal erections can be documented using mercury-filled strain gauges so that changes in penile circumference are shown as upward deflections on a strip recorder. They are associated with REM cerebral activity and normal ranges for various age groups are now known. The majority of males have 3 to 4 erections each night with 20 to 30% of the total sleep time being accompanied by penile tumescence.

N.P.T. tracings in patients with organic impotence will show absent or reduced tumescence activity, with reduced total tumescence time and also a smaller increase in penile circumference. In contrast, patients with psychogenic impotence will have normal nocturnal erections even in the complete absence of daytime erections—this makes the investigation most helpful in assessing those impotent patients where completely normal erections are absent in any situation, *e.g.* with masturbation, different sexual partner, early morning erections. Needless and unhelpful hormonal or psychiatric treatment can then be avoided in those patients with organic impotence, and such documentation is essential before considering insertion of artificial erectile prostheses.

The technique is also valuable in the documentation of penile erectile function, such as for medicolegal assessment after ruptured urethra, and before certain penile operations. For example, Peyronie's disease is now known to be associated with impotence in some patients, making N.P.T. monitoring wise before embarking on surgery for this condition, especially considering the incidence of post-operative impotence in some cases.

The ability to monitor nocturnal erections also opens up a number of new areas for research into the characteristics of penile erections, in particular the incidence of impotence with various drugs.

Transuretero-Ureterostomy

By J. C. Smith

Department of Urology and Nuffield Institute of Medical Research, Oxford, England

Transuretero-ureterostomy is probably performed less often than it should be. It is a safe and simple method of dealing with problems of the lower ureter particularly damaged by previous surgery. Fears that the opposite side may be affected by the operation have proved groundless, both in personal experience and in a questionnaire of British urological surgeons.

In a personal series of 16 cases there was one death in a patient with advanced carcinoma, the other results all being satisfactory. In 4 cases the operation was performed in a solitary kidney (or an effectively solitary kidney) and in these cases the result was particularly gratifying. In one case a ureter which had been defunctioned following nephrectomy for over 60 years provided a satisfactory result when the opposite ureter had to be removed for a neoplasm.

Place of the Free Full Thickness Skin Graft and Reconstructive Penile Surgery

By K. J. Neerhut

St John of God Hospital, Ballarat, Victoria

The use of full thickness free skin grafting in penile reconstructive surgery, as described by Devine and Horton, was discussed.

In hypospadias, one-stage correction was achieved using preputial skin for a neo-urethra. The importance of careful tissue handling, avoidance of post-operative meatal crusting, the danger of apposing suture lines and the necessity of urinary diversion and urethral splinting were all stressed.

After outlining the indications for incision, excision, patch or tube grafts in the treatment of urethral stricture, the following features in technique were stressed as being important—adequate exposure of the normal urethra, correct size of the patch, the use of Methylene Blue to define any false passages and the value of voiding post-operative urethrography. The avoidance of surgery sooner than 6 weeks following urethral instrumentation was considered important.

The application of the tube graft to a case of carcinoma of the urethra associated with urethral stricture was described. Dermal grafting in selected cases of Peyronie's disease was also briefly mentioned.

It was concluded that the techniques of free grafting described by Devine and Horton were a significant advance in urethral and penile surgery.

The Treatment of Short Urethral Strictures

By J. C. Smith

Department of Urology and Nuffield Institute of Medical Research, Oxford, England

Excision urethroplasty in a series of 42 cases from Oxford and Sheffield has proved a satisfactory method of treatment. However, in 2 of the Oxford cases strictures recurred, 7 and 5 years after operation, and in the author's view endoscopic urethrotomy is now the preferred treatment for these short strictures.

Attention is drawn to strictures occurring in the widest part of the bulb about 1 cm distal to the external sphincter where occasionally a congenital diaphragmatic stricture may be present. Strictures at this site commonly occur after transurethral resection and are often misnamed membranous strictures. It seems probable that a minimal congenital narrowing at this point is accentuated by transurethral resection and becomes obstructive. These strictures may be difficult to visualise on the urethrogram as the stricture is so short but respond well to endoscopic division.

Chordee Deformity Without Hypospadias

By E. Durham Smith

Royal Children's Hospital, Melbourne, Victoria

Chordee deformity without hypospadias is more common than generally recognised. Some deformities are very mild and represent a degree of penoscrotal skin fusion only; others are severe, with all layers of tissue being affected—urethral shortening, fibrous contraction of Buck's fascia and gross skin deficiency on the ventral side.

In the belief that urethral shortening ("congenital short urethra") was the main factor, previous surgical correction was based on division of the urethra in mid-shaft, with separation of the 2 ends, followed subsequently by penile repair of the urethral gap. Work by Devine and Horton, however, has shown that there is usually a considerable degree of elasticity or buckling in the urethra, and correction of the chordee can be achieved without dividing the urethra. The shortened deep tissues are excised and the preputial skin mobilised from the dorsum to make up the ventral skin deficiency.

A short film was shown to demonstrate the technique.

Mechanism of Anal Sphincter Stretch in the Reflex Bladder

By W. H. Donovan and A. I. Low

Royal Perth Hospital, Perth, Western Australia

Anal sphincter stretch voiding is a technique useful in some patients with reflex bladder lesions. It involves digital stretching of the anal sphincter followed by abdominal straining to produce voiding. It is carried out by the patient sitting on a commode, inserting one or two gloved fingers just through the external anal sphincter and stretching this muscle until it is felt to relax. Once this occurs, abdominal straining is used to produce voiding and is continued until the bladder is felt to be empty. It is most effective in patients whose spinal cord lesion is below the mid-thoracic level because it requires good power in the intrinsic muscles of the hand as well as adequate intra-abdominal musculature.

Kiviat and Donovan in both of their previous papers showed that after initial increase in electrical activity, anal sphincter stretch sometimes produced definite relaxation in both sphincters. It was originally thought that this was accompanied by stimulation of the detrusor contraction but later studies by these workers (subsequently confirmed by ourselves) have shown that far from stimulating the detrusor, anal stretch abolishes its activity, thereby producing a simultaneous relaxation of not only the external urethral sphincter but also the detrusor. Micturition is then achieved by raising the intra-abdominal pressure while the outflow resistance is thus lowered. This technique is currently used by 6 of our patients, 2 of whom discovered the technique for themselves during routine manual removal of faeces. All but one are mid or low thoracic spinal cord lesions and 5 of the 6 are almost completely continent, only 1 requiring to wear a urinary collecting device.

Many paraplegics with upper motor neurone lesions of their bladder have detrusor-sphincteric dyssynergia and in a number of them this produces sufficient outflow obstruction to require division of their external urethral sphincter. The use of anal stretch overcomes the necessity for this operation, and often allows virtually complete continence, a situation which is particularly important in the female in whom no satisfactory collecting device is available; 3 of our 6 patients are females.

It is a technique which we believe should be tried in all patients with spinal lesions below the mid-thoracic level as it often enables very good urinary control, along with adequate emptying, and frequently obviates the need for sphincterotomy.

Closure of the Bladder Neck for Neurogenic Incontinence

By R. R. A. Syme

Austin Hospital, Melbourne, Victoria

Female patients with spinal cord injury are usually treated by means of an indwelling urethral catheter. In the long-term this commonly leads to marked urethral dilatation, so that despite larger catheters with bigger balloons, voiding around the catheter, incontinence, catheter expulsion and bed sores occur with distressing frequency.

This problem has been overcome by operation to close the bladder neck and drain the bladder via a suprapubic catheter. It is considered safer and simpler than an intestinal conduit diversion, which is the only alternative if the problem is severe enough.

Two techniques have been evolved. An abdominal technique divides the bladder neck from the urethra and mobilises the trigone from the vagina, allowing closure of the bladder neck in layers without tension. The urethra is invaginated into itself to oppose urethral mucosa to urethral mucosa. The second and preferred technique is perineo-abdominal. This involves mobilisation of the urethra and trigone from the perineum and excision of the urethra. The bladder neck is closed and the dead space obliterated by suturing the anterior vaginal wall to the pubis. Provided there is correct catheter placement and unobstructed drainage, continence is virtually total. Patients with sufficient dexterity have been taught to change their own catheters and catheter problems have been nil.

Nine out of 10 patients healed *per primam*. One developed a small fistula which was readily closed from below.

The Significance of Asymptomatic Microscopic Haematuria

By R. R. A. Syme

Austin Hospital, Melbourne, Victoria

One hundred and forty-six patients with incidentally discovered microscopic haematuria have been investigated. They have had no pyuria, proteinuria or casts and they have had no urological symptoms that needed investigation.

All had intravenous urograms, 78% had endoscopic examination and 17% had urine cytology performed. Of the 34 patients without endoscopy, 15 had a diagnosis made without endoscopy and 4 had negative cytology.

Twenty-six per cent of the patients were under 40; 64% were between 40 and 60 and only 10% were over 60. More than half of the patients between the ages of 40 and 60 were found by multiphasic screening centres.

In 42% of the cases no diagnosis was made. Of the remainder a number of diagnoses were made, but not necessarily considered to be the cause of the haematuria. Twenty-nine per cent had evidence of minor lower tract inflammation. Thirteen per cent had mild bladder neck obstruction, while 8% had small renal calculi. Six per cent had mild non-progressive glomerulonephritis, 3% had renal cysts and 3% had renal papillary abnormalities. Only one case (less than 1%) was found to have a malignancy, a superficial transitional cell carcinoma of the bladder. The cost of discovering this was in the region of $40,000-$45,000.

These results are in sharp contrast with painless macroscopic haematuria, where malignant disease may be found in up to 48% of patients over 40.

It is therefore suggested that investigation should be considered only for persistent microscopic haematuria of more than 20,000 red cells per millilitre; endoscopy is not necessary for patients under 50, particularly if cytology is negative.

Investigation of Microscopic Haematuria in Patients Without Urologic Abnormality

By A. Tynan

Sydney, New South Wales

Increasing numbers of patients are presenting with persistent haematuria found at routine medical examinations, in whom all routine urological investigations are negative. Fifty-four patients in this series were referred for nephrological investigations. There were 30 males and 24 females with a mean age of 32 years. Twelve had hypertension and 14 impaired renal function (2 eventually died). Serious nephritis was detected in 12 and 42 had mild non-specific glomerulonephritis detected by renal biopsy. Investigation was found to be worthwhile in terms of establishing a diagnosis which aided decisions regarding subsequent employment, life insurance and superannuation as well as allowing a reasonable prognosis and institution of effective treatment.

An Overview of C.A.T. Scanning in Urological Diagnosis

By Peter T. Bruce

Queen Victoria Hospital, Melbourne, Victoria

An attempt was made to evaluate the use of computerised axial tomography as an aid in urological diagnosis. C.A.T. Scan and other methods of body imaging were placed into perspective and a comparison of their cost structure, extent of invasion, possible morbidity, patient inconvenience and relative value was made.

C.A.T. Scanning can be used as a means of differentiating between space-occupying lesions in the kidney where the lesion on an intravenous urogram is more than 1 cm in diameter. Secondly, it can be used to exclude metastatic infiltration of the renal hilar lymph nodes. Thirdly, it can help in the diagnosis of retroperitoneal pathology such as spread from a renal tumour to the retroperitoneal structures, especially the psoas muscle, and also extravasation of urine or blood in suspected renal rupture. Fourthly, where bladder carcinoma is suspected and where major surgery is contemplated, C.A.T. Scan can give valuable information with regard to spread of the tumour outside the bladder. Likewise, staging of prostatic carcinoma can also be assisted by C.A.T. Scan, often showing if the tumour has spread beyond the confines of the prostatic capsule. Finally, C.A.T. Scanning may be the most definitive pre-operative means of diagnosing renal lipoma, liposarcoma and angiolipoma.

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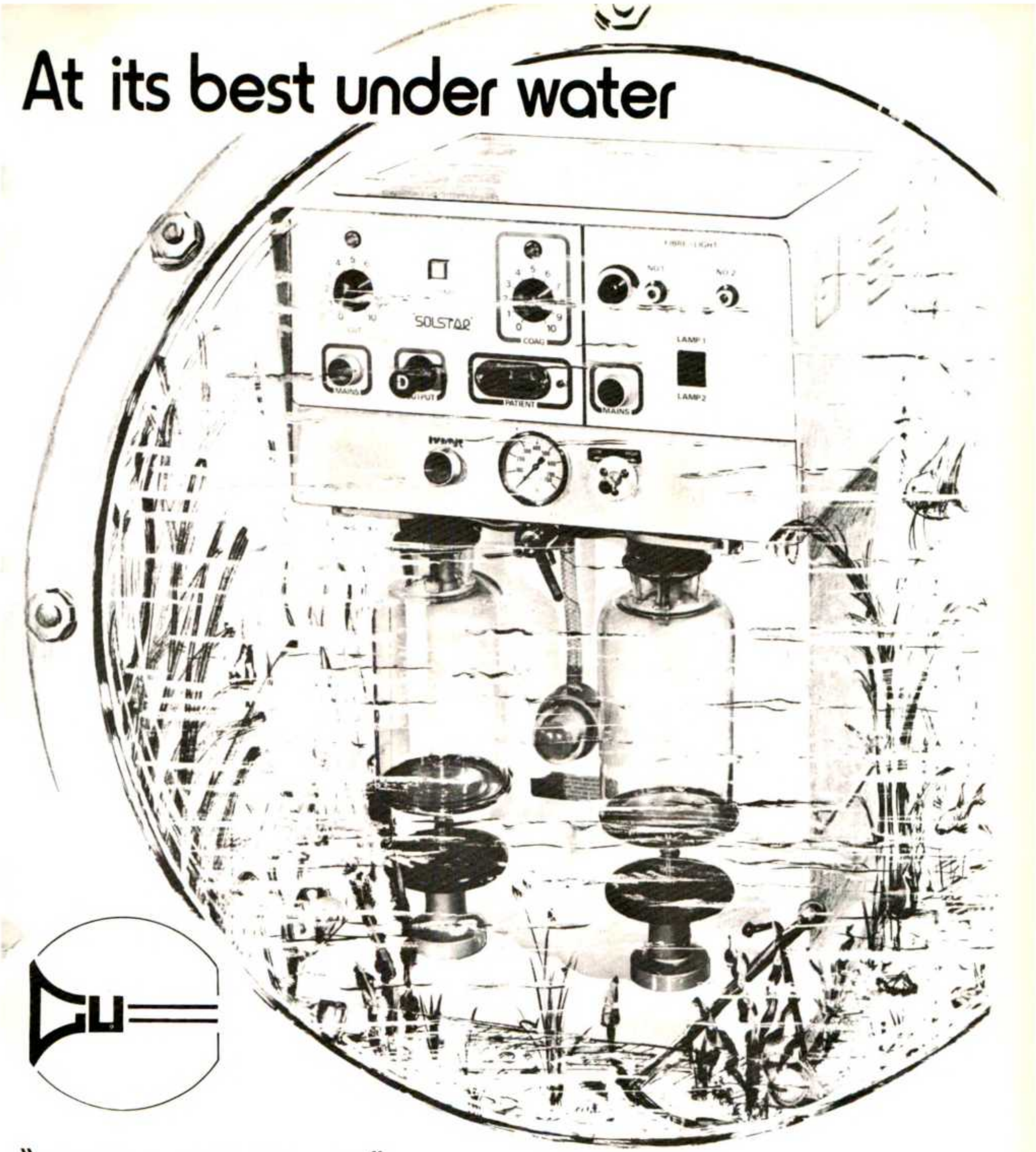

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The List of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal, i.e.* in anatomical order beginning with papers on the Adrenal.

A general section is included at the end.

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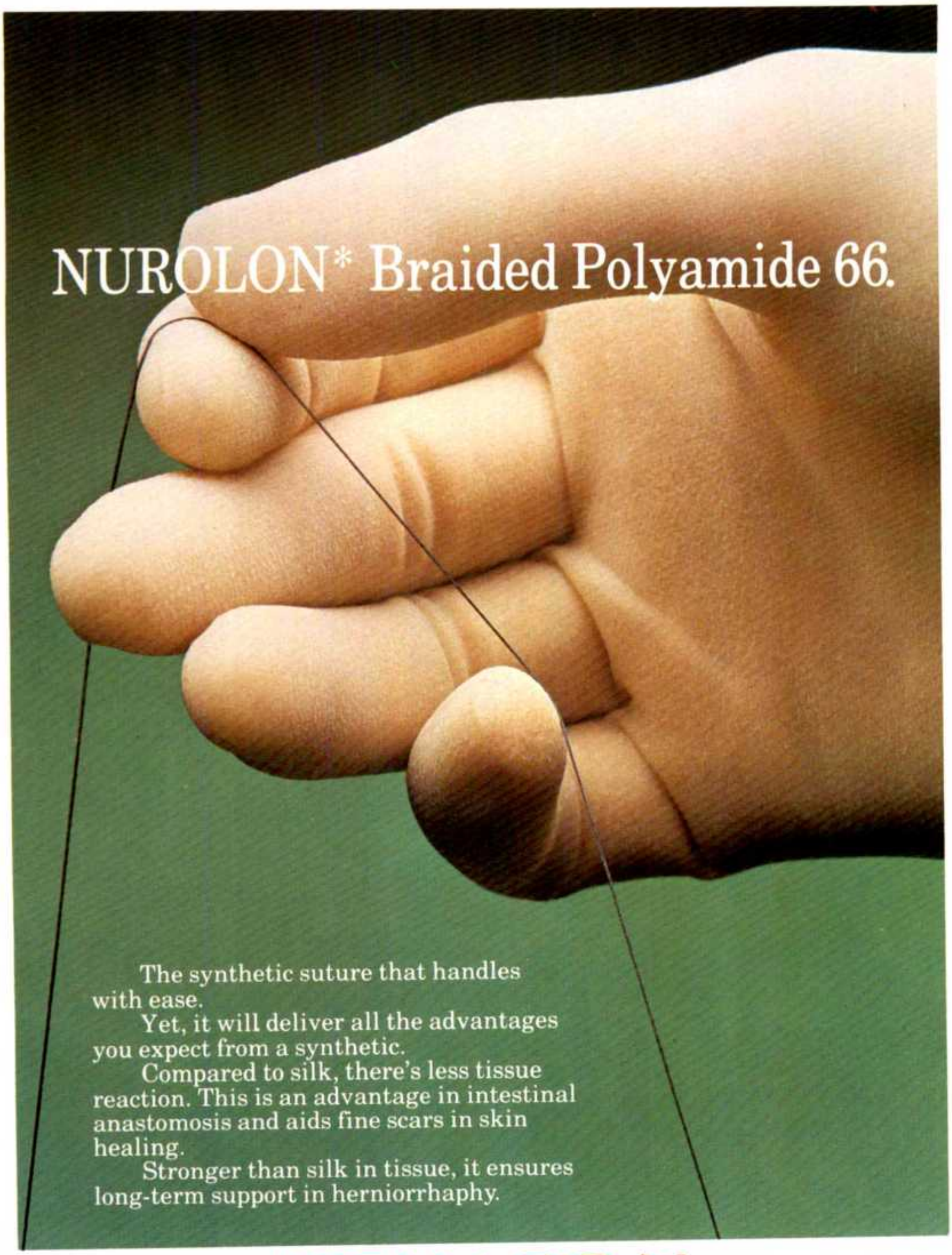

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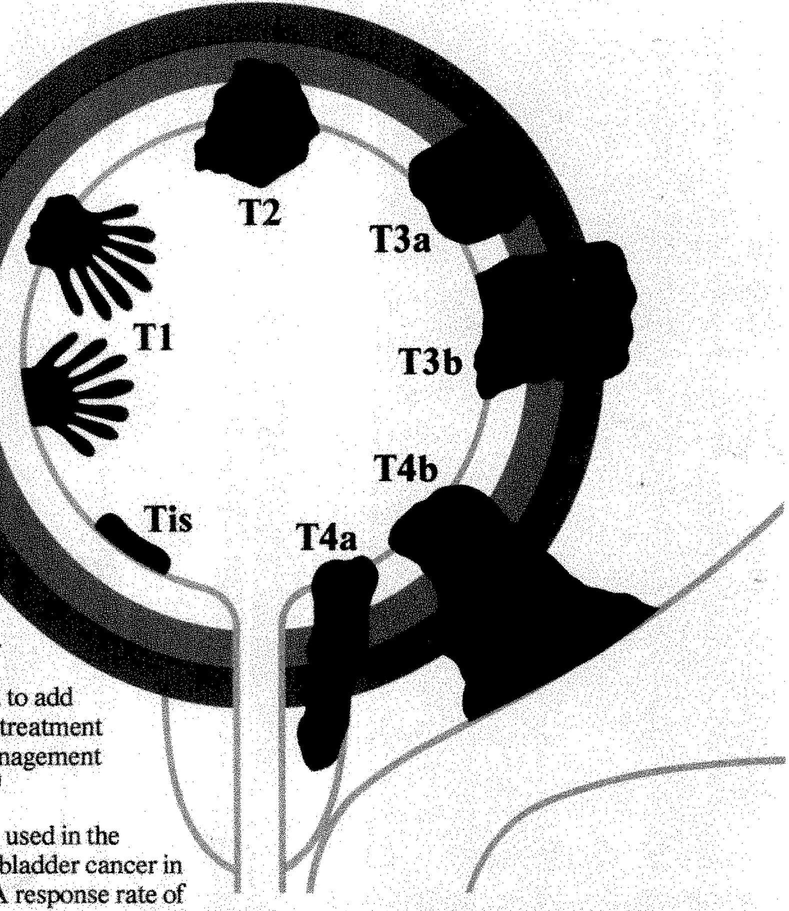
Methotrexate
in advanced bladder cancer



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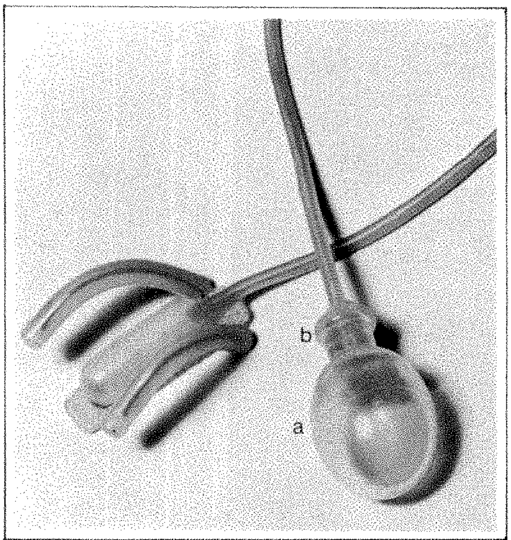

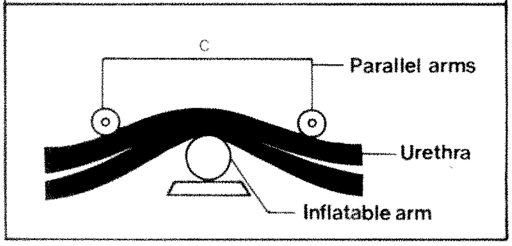

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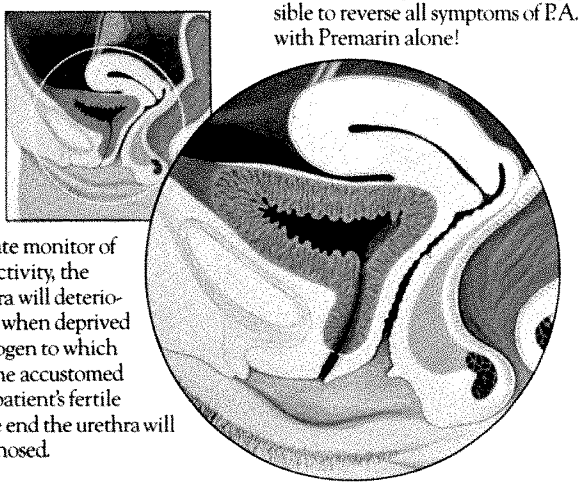

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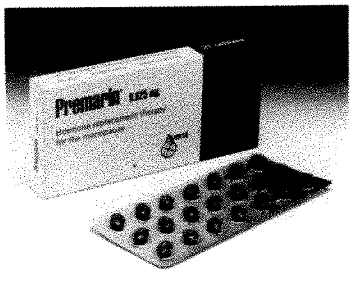

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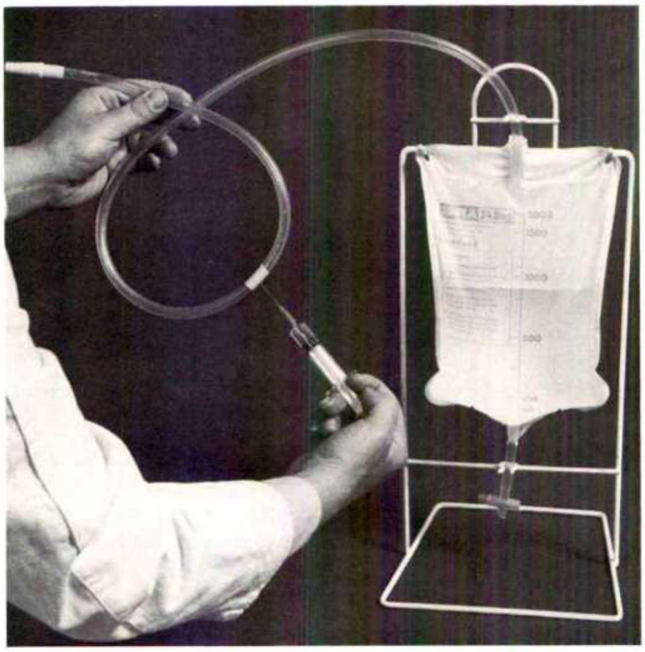

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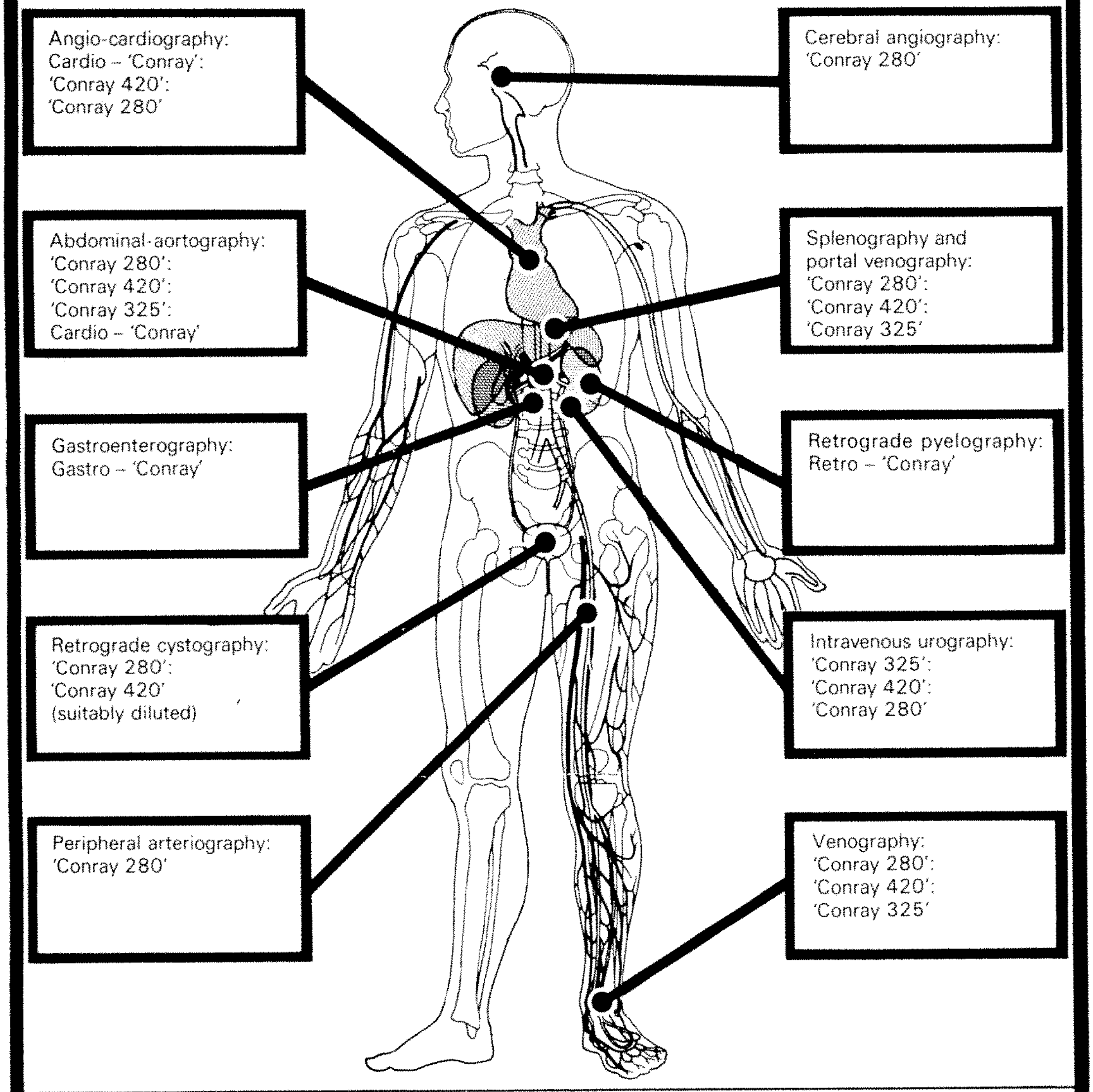

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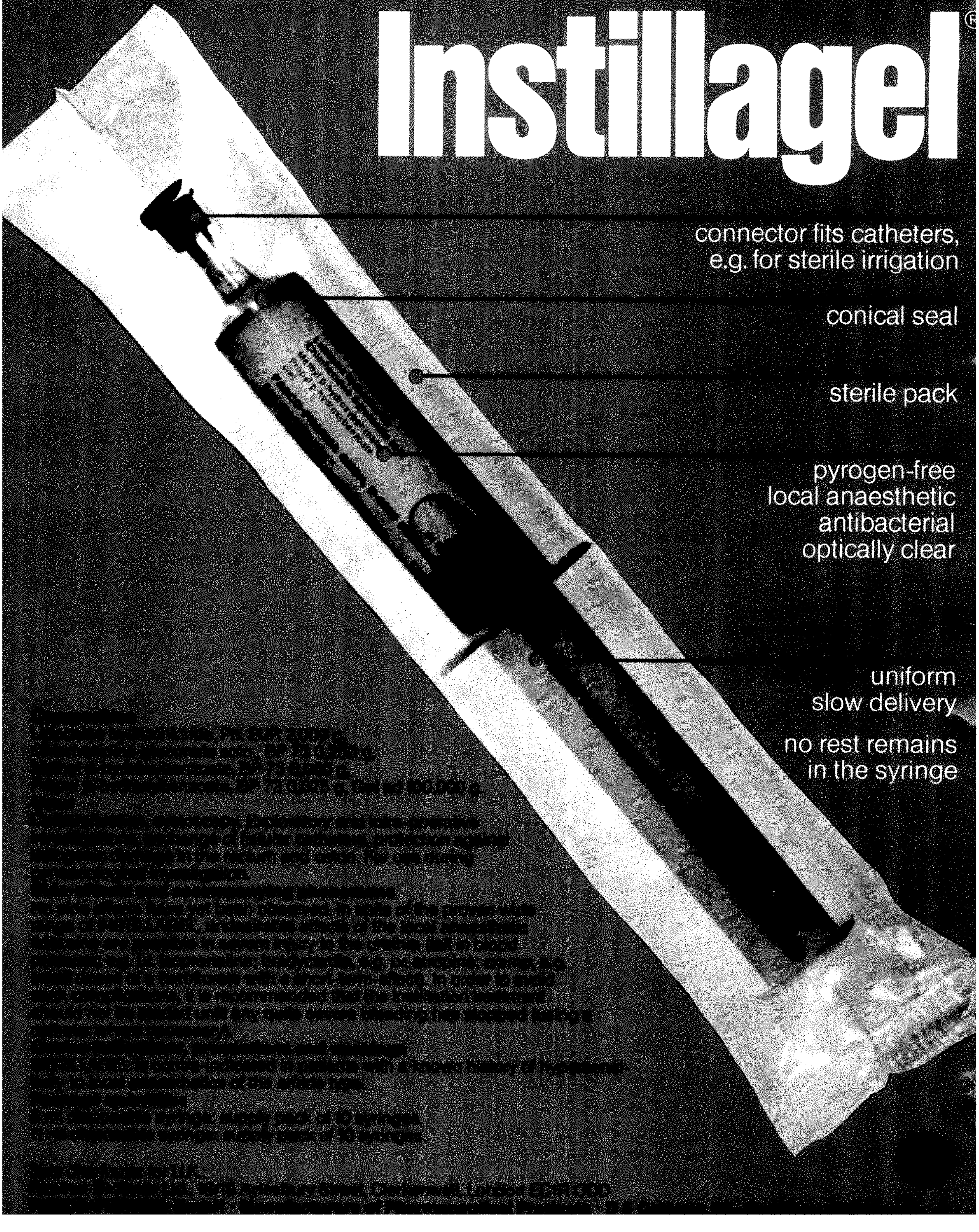

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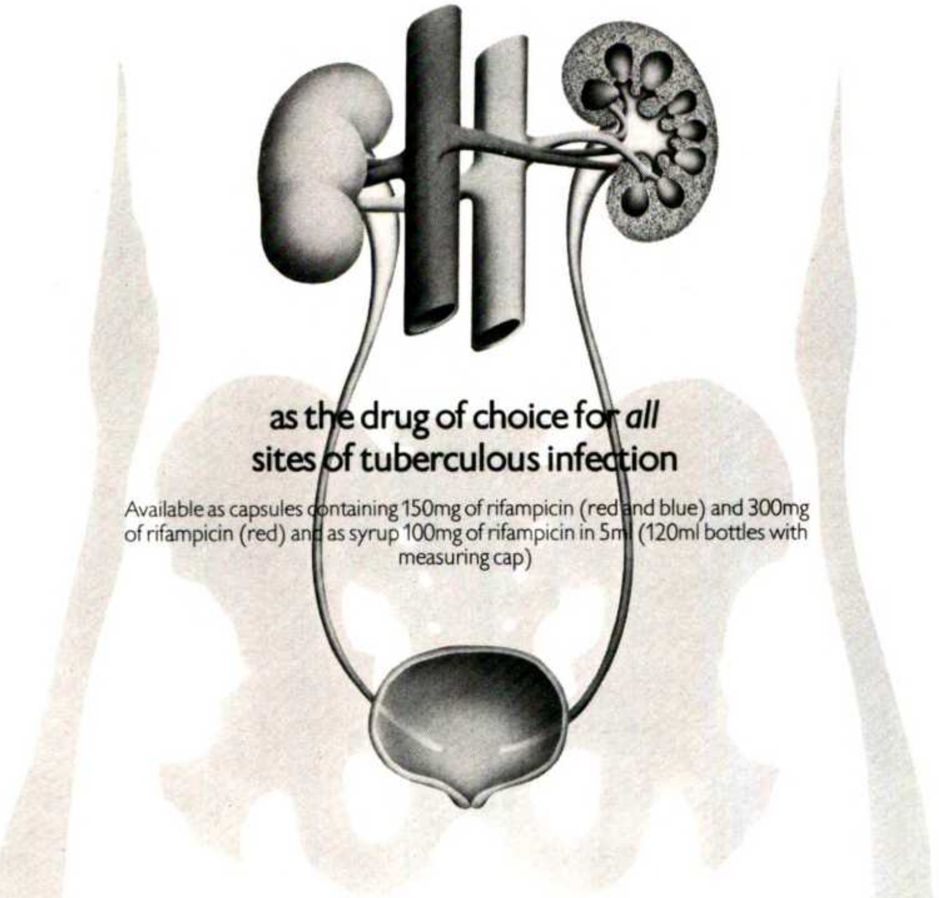

as the drug of choice for *all* sites of tuberculous infection

Available as capsules containing 150mg of rifampicin (red and blue) and 300mg of rifampicin (red) and as syrup 100mg of rifampicin in 5ml (120ml bottles with measuring cap)

Now available in calendar packs to aid patient compliance.

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Hounslow TW5 9QY
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Product Licence numbers
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Price:
150mg – Pack of 84 caps – £19.38
300mg – Pack of 56 caps – £25.82
120ml syrup – £4.48.

Lepetit

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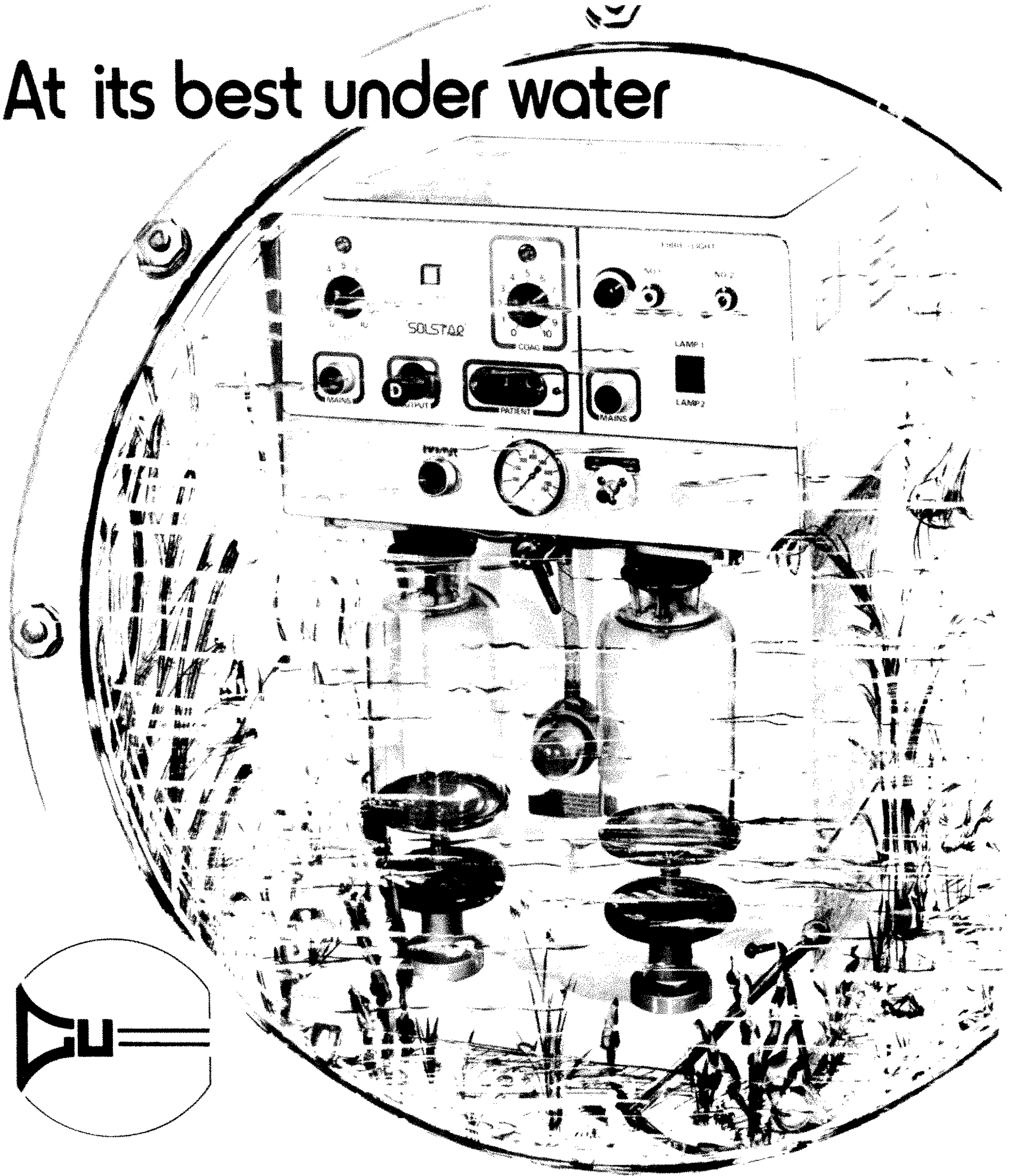
At its best under water



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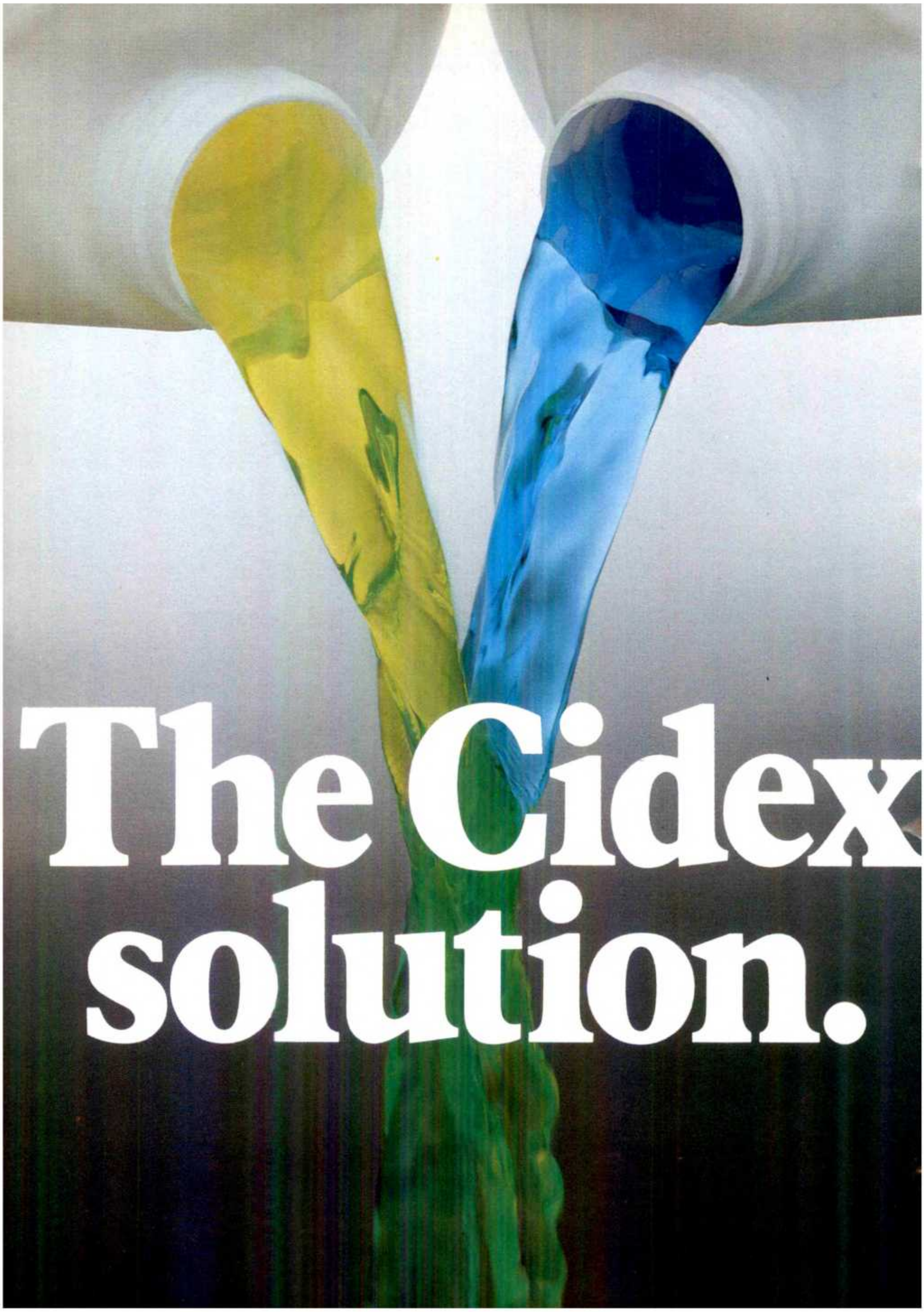

The Cidex
solution.

It has long been recognised that different hospitals have different disinfection and sterilization requirements.

These differences, of course, arise from the degree of contamination present, the type of equipment and rate of throughput, and the cleaning/drying procedures used.

What hasn't been recognised sufficiently up till now is that these factors combine to have a cumulative effect on the use-life of cold disinfectant solutions–creating a need for solutions with different use-lives.

To meet this need there are now two solutions.

–CIDEX* Activated Glutaraldehyde Solution with a use-life of up to 14 days.

–CIDEX* Long-Life Activated Glutaraldehyde Solution with a use-life of up to 28 days.

New CIDEX* Long-Life Solution has all the trusted and well-proven benefits of 14 day CIDEX* Solution but has an effective life of 28 days where usage factors permit.

A fresh peppermint odour and blue colour differentiate CIDEX* Long-Life from green 14 day CIDEX* Solution.

WHICH CIDEX* SOLUTION TO USE

While the effects of dilution and gross protein contamination are always present, these can be minimal due to low throughput.

Under these circumstances, new CIDEX* Long-Life Solution is much more convenient and can offer substantial cost savings.

In a busy unit, however, where pressures generally do not permit drying, protein contamination and dilution can build up over a period–particularly with bulky items, such as anaesthetic tubing, which have a high carry-over of water.

In situations such as this, 14 day CIDEX* Solution offers complete assurance of its efficacy, assurance which has been confirmed repeatedly all over the world.

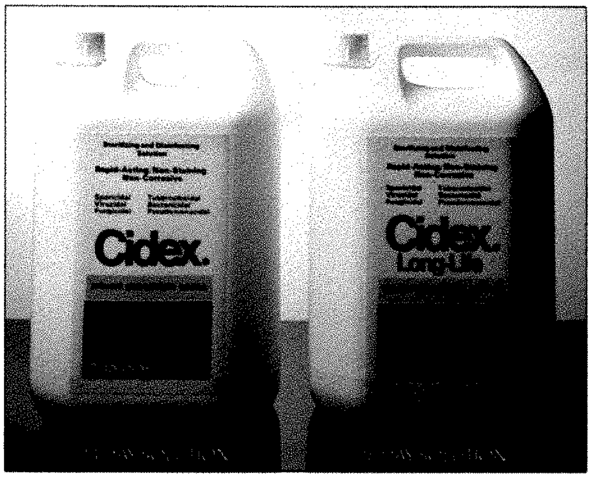
CIDEX* SOLUTIONS. NOT ONLY A CHOICE BUT A BETTER CHOICE

Both solutions have the complete range of cidal activity which has made CIDEX* Solution the prime agent of choice for disinfection and sterilization of heat sensitive and delicate equipment.

Both have the remarkable non-corrosive properties which in laboratory tests have proven them to be less corrosive than deionised water.

14 day CIDEX* Solution in the green container. 28 day CIDEX* Long-Life Solution in the blue container.

Whatever your choice, you can be confident that CIDEX* is the safest, most cost-effective solution to your disinfecting or sterilizing problem.



A choice of CIDEX* solutions from Arbrook – now you can choose wisely.

Arbrook*

Cinobac. Power to fight (Cinoxacin) urinary tract infections.

Cinobac is the potent new oral therapy for chronic and acute urinary tract infections with a 96% success rate – including recurrent infections.[1]*

Cinobac combines powerful relief with a low incidence of side-effects in cystitis, pyelonephritis, pyelitis and asymptomatic bacteriuria.

A powerful antibacterial action[1]

Cinobac, a carboxylic acid derivative, is metabolised less than nalidixic acid, oxolinic acid and sulphamethoxazole, and therefore active concentrations in urine are higher than with any of these other drugs.

In the studies conducted, of all pathogens isolated in urine, less than 3% were resistant to Cinobac.

Low on side-effects

In 26 clinical trials 1118 patients received Cinobac; investigators confirm the view that Cinobac is free from unpleasant side-effects, and is well tolerated in the treatment of urinary tract infections.[2,3,4]

Cinobac – a simple 500 mg b.d. dosage in a convenient calendar pack to aid compliance.

CINOBAC

CINOXACIN

Prescribing Information

"CINOBAC" Cinoxacin INN

Presentation

Capsules containing 500 mg cinoxacin INN PC.

Uses

CINOBAC is indicated in acute, recurrent and chronic upper and lower urinary tract infections due to susceptible micro-organisms.

Dosage & Administration

CINOBAC is administered orally. The usual adult dose is 1 g daily in two divided doses.

Contra-indications

Cinoxacin is contra-indicated in patients with a history of hypersensitivity to cinoxacin.

Warnings

The use of cinoxacin is not recommended during pregnancy, for the nursing mother, or for children as safety has not been established.

Precautions

CINOBAC is not recommended for patients with severely impaired renal function and should be used with caution in patients with reduced renal function.

Adverse Reactions

Gastro-intestinal – nausea, anorexia, vomiting, abdominal cramps and diarrhoea have been reported.

Hypersensitivity – rash, itching, urticaria and peripheral and oral oedema have occurred.

Other adverse reactions possibly related to cinoxacin include dizziness, headache, insomnia, tingling sensation, perineal burning, photophobia and tinnitus.

Transient changes in AST (SGOT), ALT (SGPT), BUN, ALP and creatinine clearance have been observed occasionally.

Product licence

PL 0006/0124

Basic NHS Cost ex calendar pack 68p per day.

References

1. Current Chemotherapy (Proceedings of the 10th International Congress of Chemotherapy), II, 1041. American Society for Microbiology, 1978.
2. Current Chemotherapy (Proceedings of the 10th International Congress of Chemotherapy), I, 704. American Society for Microbiology, 1978.
3. Proceedings of the 9th International Chemotherapy Congress, 1976, 5: 417.
4. Antimicrobial Agents and Chemotherapy, 1976, 9: 502.

*Including patients with physical abnormalities of the urinary tract.

Further information is available on request,
Eli Lilly and Company Limited,
Basingstoke, Hants RG21 2XA.

DISA

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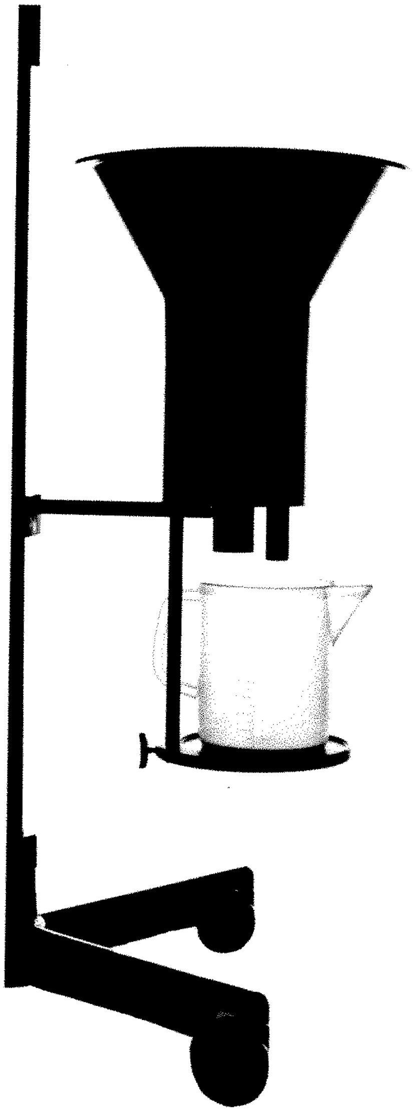
Urodynamics



DISA **TECHNO HOUSE · REDCLIFFE WAY · BRISTOL BS1 6NU**
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In urinary tract infections

New ipral™

trimethoprim 100 mg

...the way to effective treatment of urinary tract infections

Trimethoprim – proved effective as a single entity without the side-effects associated with sulphonamides.

"Trimethoprim alone may well prove as effective as trimethoprim-sulphamethoxazole combinations ..."[1]

96% success in general practice.[2] Half as many side-effects.

Results of 107 Courses of Treatment in 96 Domiciliary Patients

Antibiotic	Overall Success
Ampicillin	89%
Cephalexin	62%
Co-trimoxazole	81%
Trimethoprim	96%

ipral simple treatment for acute infections – 2 tablets b.d.

ipral for routine use in chronic U.T.I. – 1 tablet b.d.

In a study on recurrent U.T.I.'s
"... trimethoprim is the most effective of the antibacterial agents examined."[3]

Greater efficacy with fewer side effects.

In the trial in acute U.T.I.'s
"... the total side effects caused by ampicillin, cephalexin and co-trimoxazole were similar and occurred twice as often as when trimethoprim was given alone ..."[2]

Antibiotic	No. of Patients	% Side Effects
Ampicillin	88	22
Cephalexin	84	25
Co-trimoxazole	83	21
Trimethoprim	**84**	**8**
Total	339	

Prescribing information

IPRAL tablets
Each tablet contains trimethoprim B.P. 100 mg.

Indications
Ipral is indicated for the treatment and prophylaxis of acute and chronic urinary tract infections.

Actions
Ipral is active in-vitro against most pathogenic Gram-positive and Gram-negative bacteria. Exceptions include Neisseria species and Pseudomonas aeruginosa.

Dosage and administration
For acute urinary tract infections 2 tablets twice daily is recommended. For long term and prophylactic therapy 1 tablet twice daily is recommended.

Contra-indications
Ipral should not be given to patients with severe renal insufficiency where blood levels cannot be monitored regularly. Ipral should not be used in pregnancy or during the first few weeks of life.

Precautions
Care is necessary in administration to patients with impaired renal function. Special precaution should be exercised in patients with a predisposition to folate deficiency.

Side-effects
Nausea, vomiting and skin rashes may occur but are rare. Ipral may depress haematopoiesis during prolonged therapy. This has proved reversible when treated with calcium folinate.

Treatment of overdosage
Gastric lavage. Calcium folinate may be used to counteract any effect of Ipral on bone-marrow.

Package quantities and price
Packs of 100 tablets £5.30.
Product Licence No. - 0034/0190.

Full prescribing information available from:
Technical Services Department, E. R. Squibb & Sons Ltd.
Regal House, Twickenham, TW1 3QT
Tel: 01-892 0164

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Ipral is a Trade Mark of E. R. Squibb & Sons Ltd

...the way to effective treatment of urinary tract infections

- As effective as trimethoprim/sulphamethoxazole combination
- Avoids the side effects of sulphonamides
- At a sensible price

and "Trimethoprim given alone was shown to be much better tolerated."[2]

"Treatment with TMP (trimethoprim) alone is superior to the combined regimen due to a smaller incidence of side-effects; ..." thus "... introduction of TMP alone on the market is recommended."[4]

"Less gastrointestinal side-effects and skin rashes have occurred with trimethoprim ..."[3]

References
1. Lancet 1979, **1**, 493. 2. Br. med. J. 1972, **2**, 673.
3. Ann. clin. Res. 1978, **10**, (suppl. 22). 4. Chemother. 1973, **19**, 314.

New
ipral™
trimethoprim 100 mg
more than half the story

SQUIBB™ Full prescribing information available from: Technical Services Department, E. R. Squibb & Sons Ltd. Regal House, Twickenham, TW1 3QT Tel: 01-892 0164

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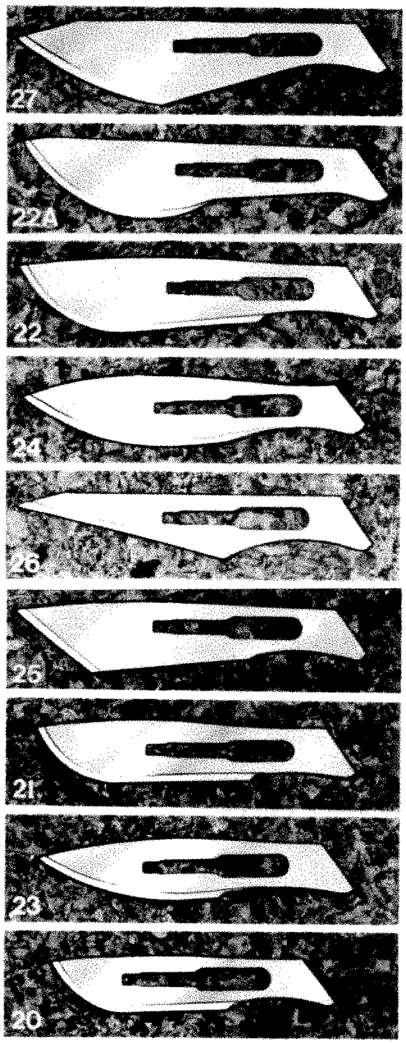
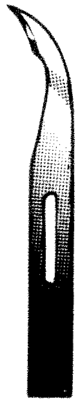
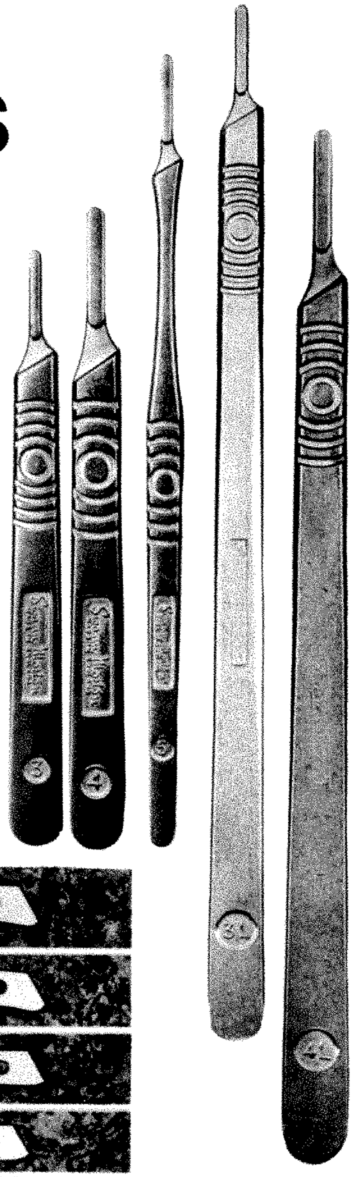
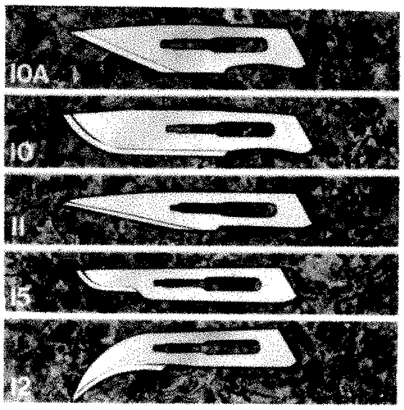
...the choice of surgeons the world over. The Swann-Morton range of stainless and carbon steel blades includes all the nine universally accepted shapes.





STITCH CUTTER requires no handle and eliminates the use of scissors.



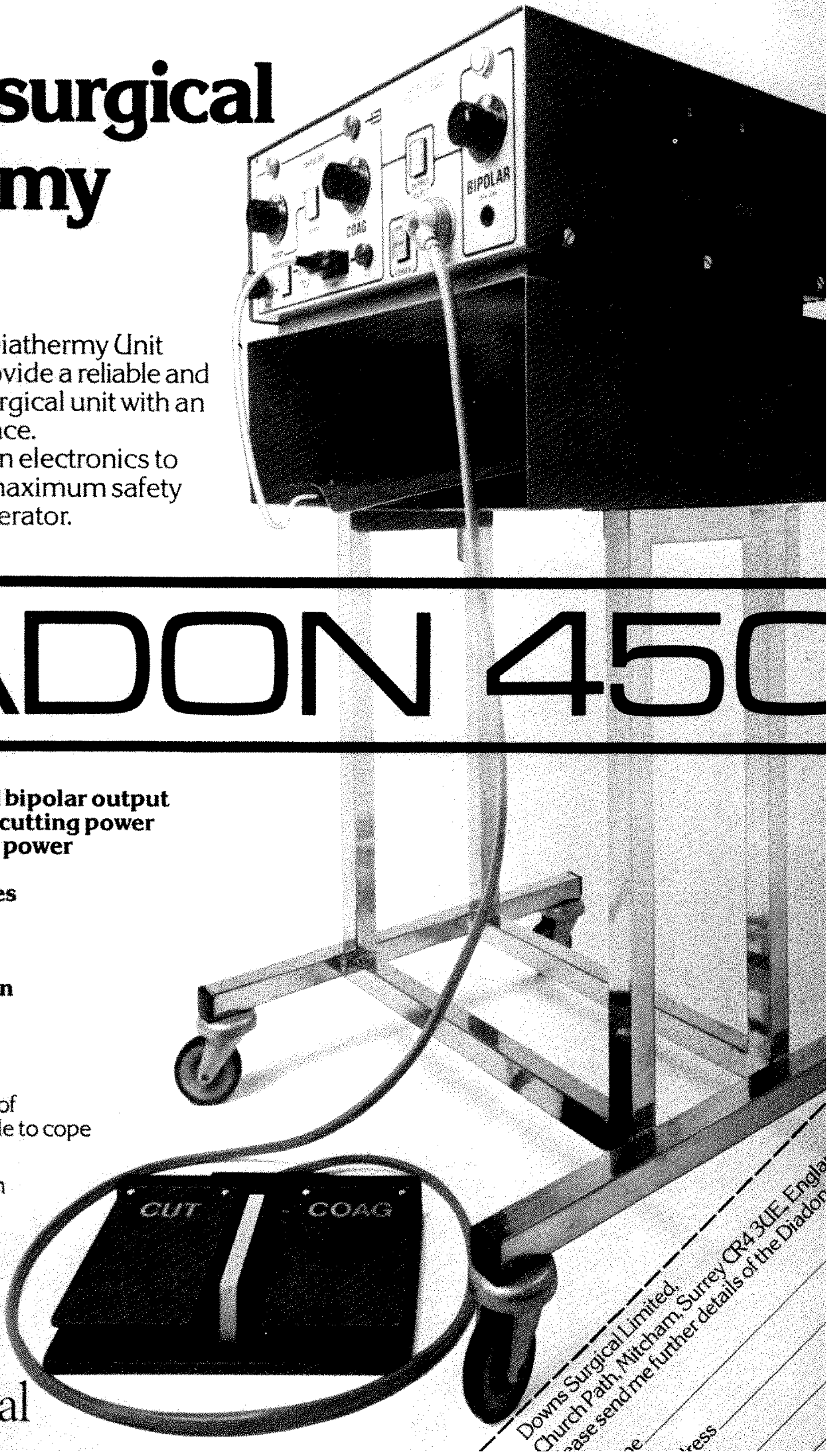


Swann-Morton

Swann-Morton Limited
Penn Works, Owlerton Green, Sheffield S6 2BJ
Telephone: 0742-344231 Telex: 547538.

Diadon 450. A New Electrosurgical Diathermy Unit.

The New Diadon 450 Diathermy Unit has been created to provide a reliable and simple to use electrosurgical unit with an outstanding performance.
The unit utilises modern electronics to provide conditions of maximum safety to both patients and operator.



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- ☐ **Powerful unipolar and bipolar output 400 watts continuous cutting power 125 watts coagulating power**
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Diadon 450 is suitable for continual use in the busiest of operating theatres and is able to cope with all surgical specialities.

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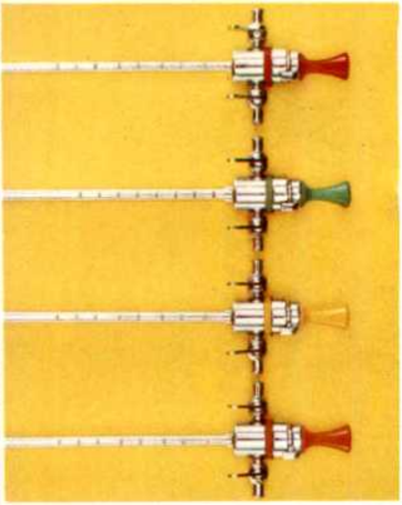
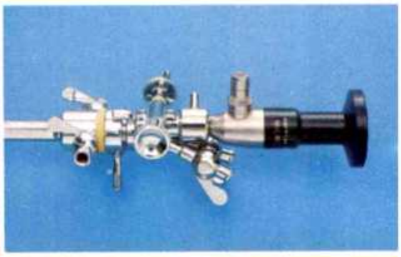
hone or write for full literature, or better still, ask for a demonstration.





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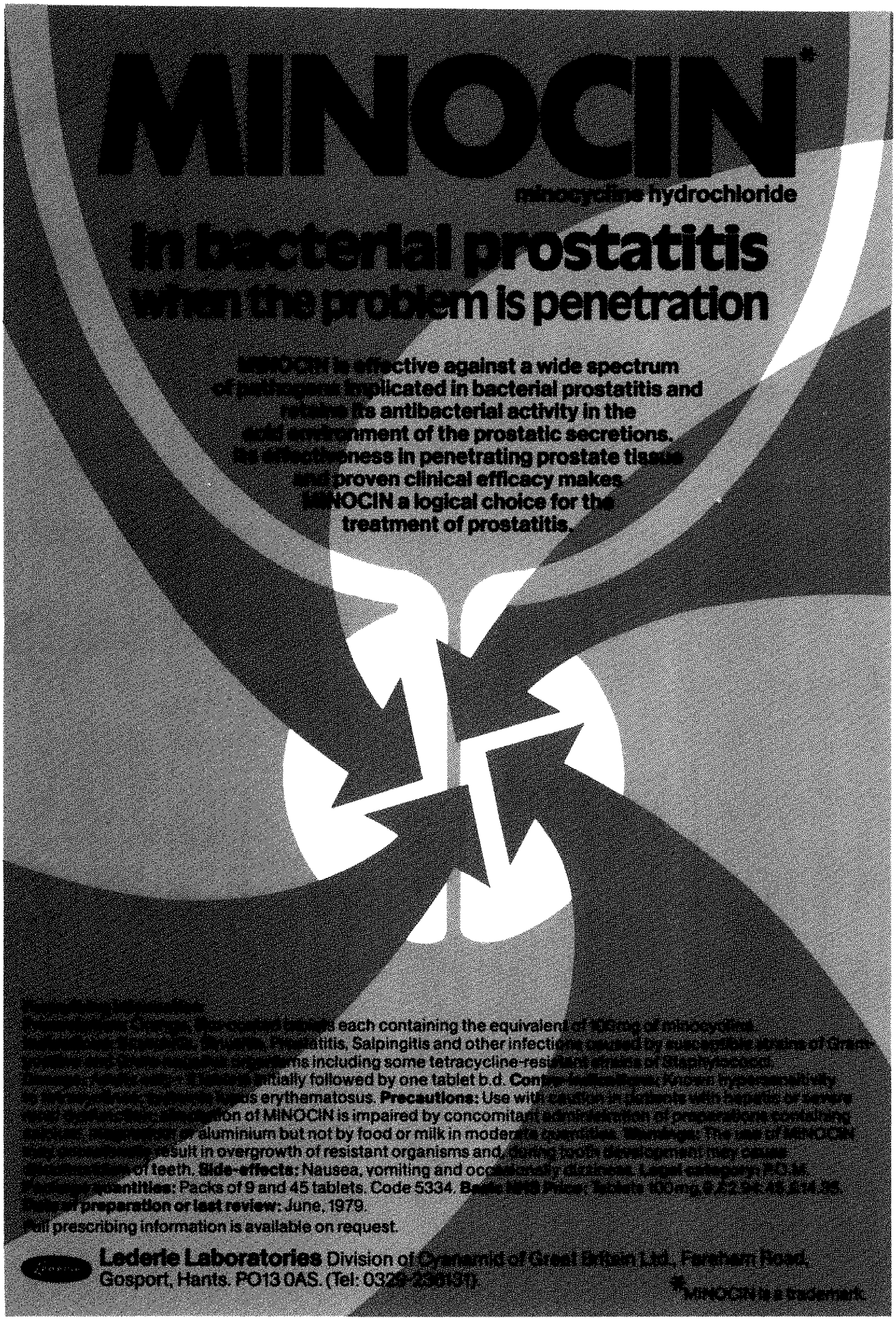


MINOCIN*

minocycline hydrochloride

In bacterial prostatitis
when the problem is penetration

MINOCIN is effective against a wide spectrum
of pathogens implicated in bacterial prostatitis and
retains its antibacterial activity in the
acid environment of the prostatic secretions.
Its effectiveness in penetrating prostate tissue
and proven clinical efficacy makes
MINOCIN a logical choice for the
treatment of prostatitis.

Prescribing Information.
Presentation: Orange, film-coated tablets each containing the equivalent of 100mg of minocycline. **Indications:** Bronchitis, Sinusitis, Prostatitis, Salpingitis and other infections caused by susceptible strains of Gram-positive and Gram-negative organisms including some tetracycline-resistant strains of Staphylococci. **Dosage:** Adults only: 2 tablets initially followed by one tablet b.d. **Contra-indications:** Known hypersensitivity to tetracyclines. Systemic lupus erythematosus. **Precautions:** Use with caution in patients with hepatic or severe renal dysfunction. Absorption of MINOCIN is impaired by concomitant administration of preparations containing calcium, magnesium or aluminium but not by food or milk in moderate quantities. **Warnings:** The use of MINOCIN may occasionally result in overgrowth of resistant organisms and, during tooth development may cause discolouration of teeth. **Side-effects:** Nausea, vomiting and occasionally dizziness. **Legal category:** P.O.M. **Package quantities:** Packs of 9 and 45 tablets. Code 5334. **Basic NHS Price:** Tablets 100mg 9 £2.94, 45 £14.35. **Date of preparation or last review:** June, 1979.
Full prescribing information is available on request.

Lederle Laboratories Division of Cyanamid of Great Britain Ltd., Fareham Road,
Gosport, Hants. PO13 0AS. (Tel: 0329-236131).

*MINOCIN is a trademark.

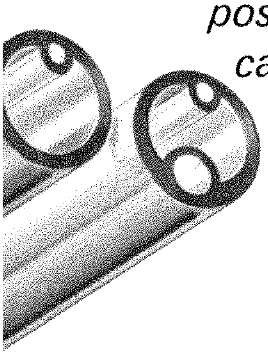
Simplastic less catheter...

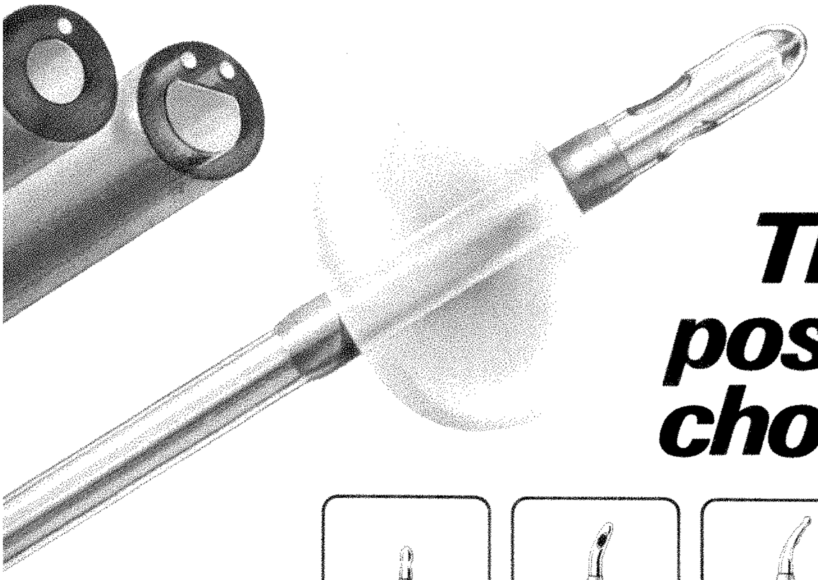
Simplastic foleys provide the optimum combination of properties for postoperative use, and are clearly superior to latex catheters.

With Simplastic, extremely thin walls mean a correspondingly wide lumen, giving high flow rates and minimising the risk of blockage with postoperative debris. But if blockage does occur, Simplastic catheters withstand suction without collapse.

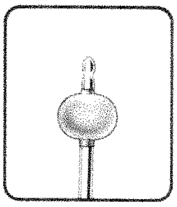
Thermoplastic PVC is firm enough for easy insertion, but softens at body temperature for patient comfort.

Available as two or three-way irrigation catheters, with a wide range of tips for specialist applications.

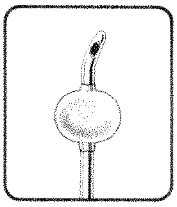




The logical postoperative choice



Two opposed



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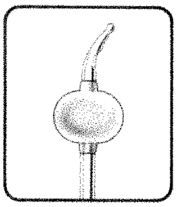
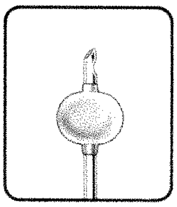
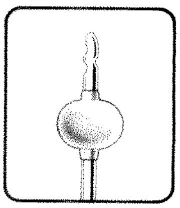


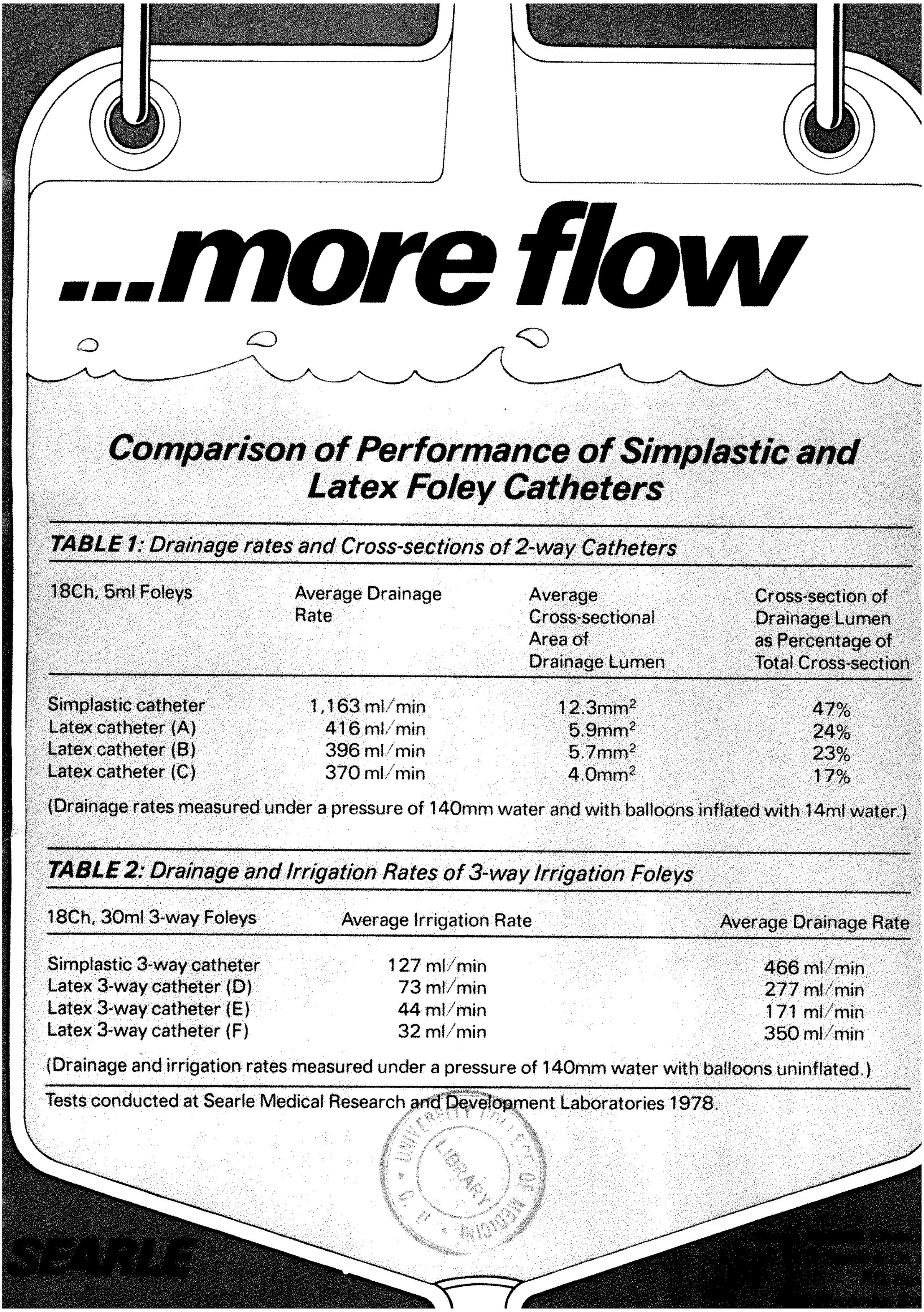
Tiemann



Whistle



Three-way



...more flow

Comparison of Performance of Simplastic and Latex Foley Catheters

TABLE 1: *Drainage rates and Cross-sections of 2-way Catheters*

18Ch, 5ml Foleys	Average Drainage Rate	Average Cross-sectional Area of Drainage Lumen	Cross-section of Drainage Lumen as Percentage of Total Cross-section
Simplastic catheter	1,163 ml/min	12.3mm^2	47%
Latex catheter (A)	416 ml/min	5.9mm^2	24%
Latex catheter (B)	396 ml/min	5.7mm^2	23%
Latex catheter (C)	370 ml/min	4.0mm^2	17%

(Drainage rates measured under a pressure of 140mm water and with balloons inflated with 14ml water.)

TABLE 2: *Drainage and Irrigation Rates of 3-way Irrigation Foleys*

18Ch, 30ml 3-way Foleys	Average Irrigation Rate	Average Drainage Rate
Simplastic 3-way catheter	127 ml/min	466 ml/min
Latex 3-way catheter (D)	73 ml/min	277 ml/min
Latex 3-way catheter (E)	44 ml/min	171 ml/min
Latex 3-way catheter (F)	32 ml/min	350 ml/min

(Drainage and irrigation rates measured under a pressure of 140mm water with balloons uninflated.)

Tests conducted at Searle Medical Research and Development Laboratories 1978.

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A new approach to the problem of treatment of oestrogen-resistant carcinoma of the prostate.

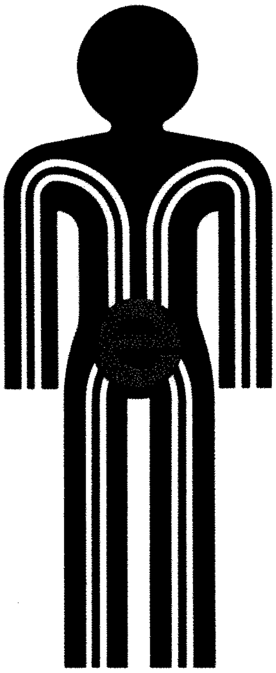
ESTRACYT*

estramustine phosphate

A unique compound
Estramustine phosphate (Estracyt) is a chemical compound of normustine and oestradiol. It utilises the concept of oestrogen as a carrier of the inert cytotoxic agent to the target tissue (with a high affinity for oestrogens) where cleavage of the molecule releases active normustine.

With a unique action
Estracyt appears to have specific affinity for, and effect on, prostate tissue but to have only weak systemic cytotoxic effects; thus long-term administration can be tolerated.

With unique results
In oestrogen-resistant carcinoma of the prostate, published results of treatment of over 500 patients with Estracyt relate to 80% with Stage IV disease and 20% Stage III. They show that SUBJECTIVE response to treatment, seen in 40% to 65% of oestrogen-resistant patients,[1,2] usually occurs within 14 days, relief of pain being the most obvious benefit. OBJECTIVE responses were seen in 19%–48% of patients with advanced disease.[3,4]



Indications. Carcinoma of the prostate, especially in cases unresponsive to, or relapsing after conventional oestrogen therapy or orchidectomy.
Dosage and Administration. The adult dose ranges from 1 to 10 capsules a day by mouth, with meals. Standard starting dose 4 capsules a day with later adjustment according to response. One to 2 capsules a day may be adequate for maintenance therapy.
Precautions. Caution in administration to patients with moderate to severe bone marrow depression.
Adverse Reactions. Commonly transient nausea, occasionally vomiting and rarely diarrhoea, gynaecomastia, angina, rash and/or fever, transient disturbance of liver function.
Contraindications. Peptic ulceration, severe liver disease or severe cardiac disease. Children.
Pharmaceutical Precautions. Store in cold place (2°C to 8°C).
Package Quantities. Bottles of 100 capsules.
P.L.No. 0458/0016
P.A.No. 115/3/1

Lundbeck

Further information and data sheet
are available from Lundbeck
Limited, Lundbeck House, Hastings
Street, Luton Beds. LU1 5BE

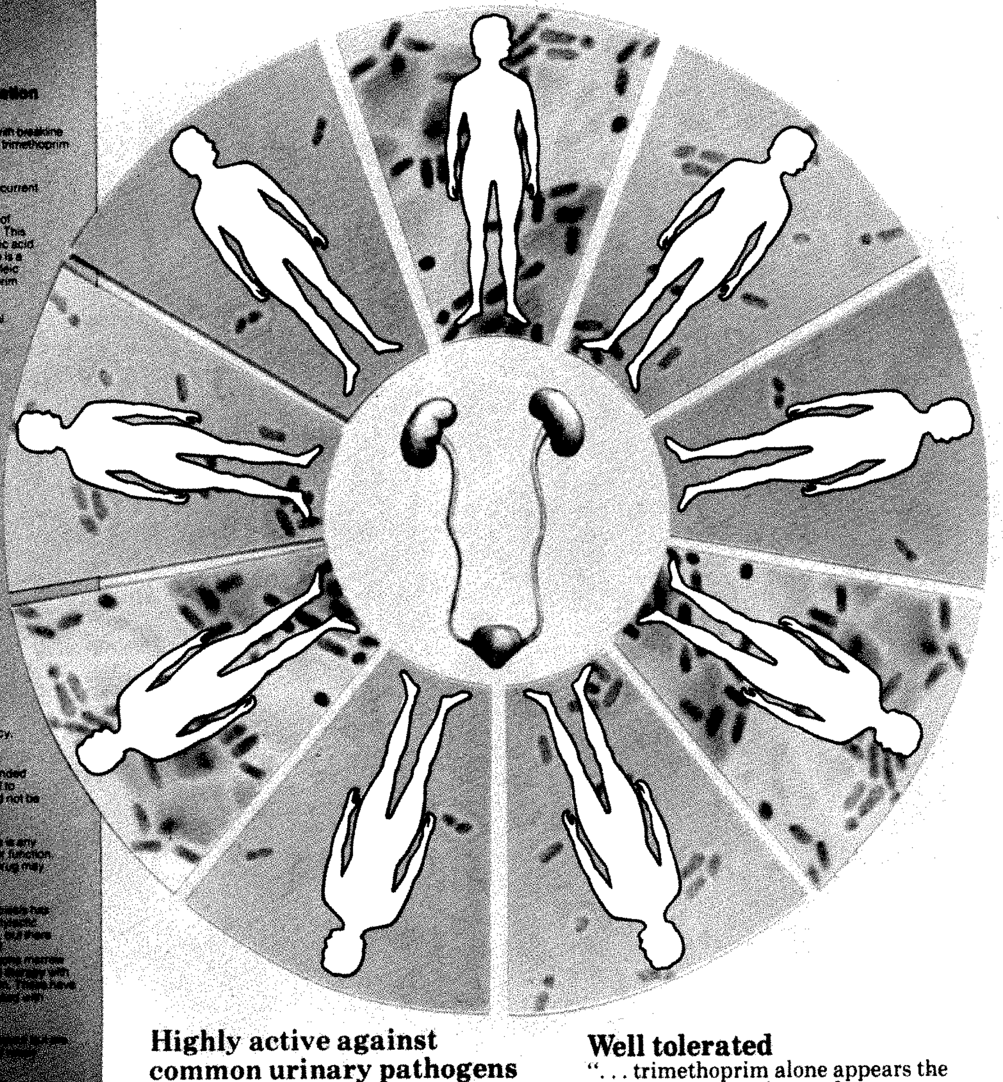
References
1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., 49, 73-79. 2. Mayer, E.J. Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, 32, 114-119. 3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., 111: 231-238. 4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

* Trade Mark

TRIMOPAN*

trimethoprim

effective prophylaxis in recurrent urinary tract infection



Prescribing information

Presentation
White tablets 9mm diameter with breakline on reverse, each containing trimethoprim B.P. 100mg.

Uses
Long-term prophylaxis of recurrent urinary tract infection.

Trimethoprim is an inhibitor of dihydrofolic acid reductase. This enzyme converts dihydrofolic acid to tetrahydrofolic acid which is a precursor of deoxyribonucleic acid. The effect of trimethoprim on folic acid synthesis is 50,000 times weaker in human cells than in bacterial cells. Trimethoprim has a range of activity very similar to that of sulphonamides but, in vitro most organisms show a far higher sensitivity to trimethoprim. The only common bacterium resistant to trimethoprim is Pseudomonas. Whereas enterobacter, E-coli, Proteus and Klebsiella are trimethoprim-sensitive. Likewise trimethoprim is suitable for the therapy of Streptococcus faecalis infections. Gonococcus is trimethoprim-resistant.

Dosage and administration
Adults: For the prophylaxis of recurrent urinary tract infection, one tablet each night before bed.
Children: Paediatric dosage for prophylaxis has not been established.

Contra-indications
Serious hepatic or renal dysfunction, folate deficiency, blood dyscrasias.
Although there is no clinical evidence that the recommended dose of Trimopan is harmful to the foetus, Trimopan should not be used in pregnancy.

Precautions
[illegible] when there is any [illegible] kidney or liver function [illegible] of the drug may [illegible]

[illegible]

Highly active against common urinary pathogens
"The most common gram-negative bacilli, E. coli, Proteus and Klebsiella are sensitive to trimethoprim . . . Pseudomonas is resistant."(1)

Extensive clinical experience – low relapse/reinfection rates(1)
"[Trimopan] . . . has been used for more than 600,000 months of treatment, i.e. 50,000 patient years."(1)

Low incidence of resistance
"The percentage of trimethoprim-resistant strains in clinical practice has not increased remarkably during recent years."(1)

Well tolerated
". . . trimethoprim alone appears the safest of all drugs [tested] against urinary tract infection."(1)

Convenient once daily dosage
Simply – one 100mg tablet nightly.

for recurrent U.T.I.

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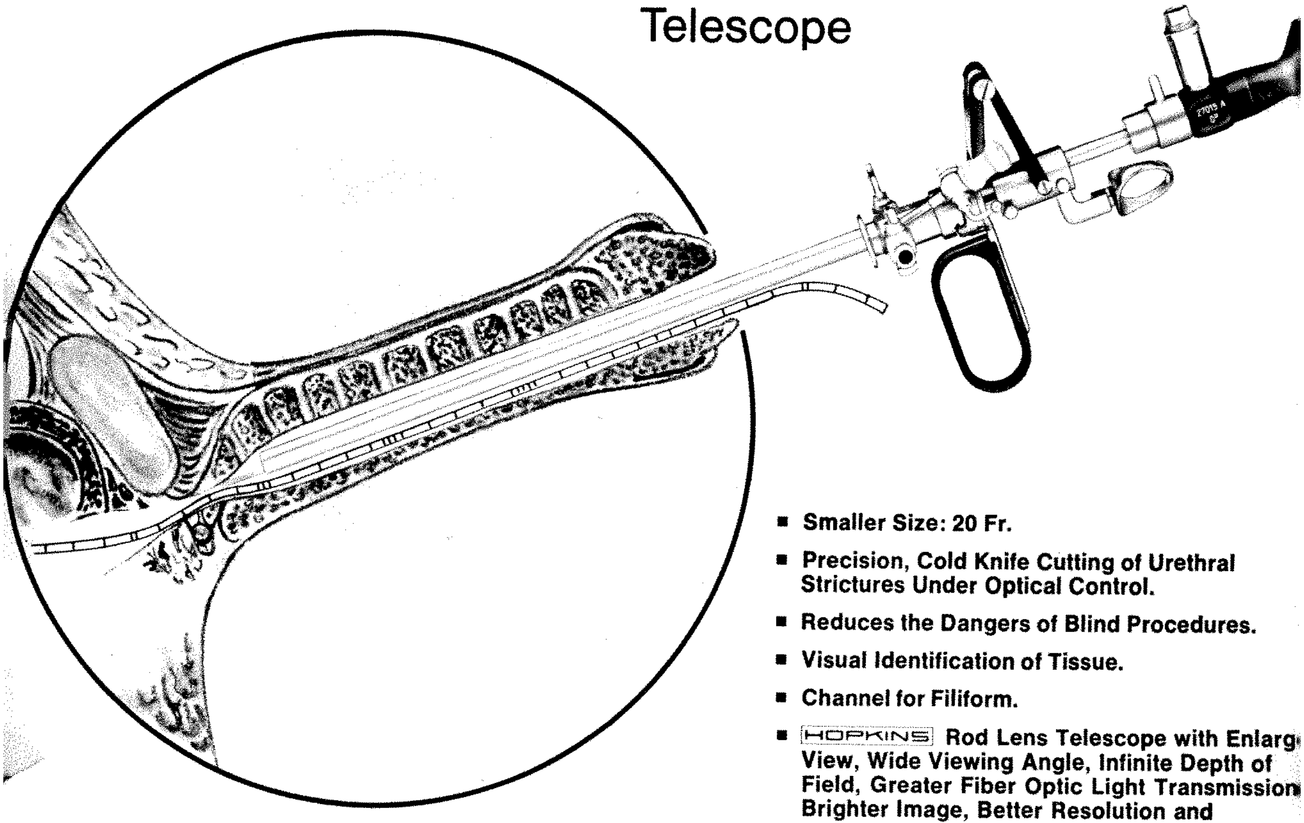

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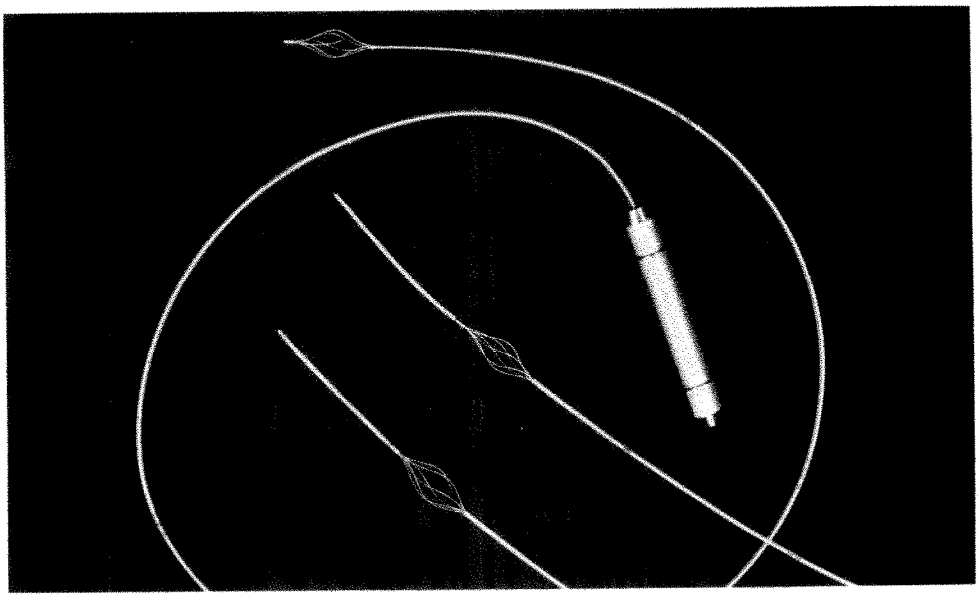

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British Journal of Urology (1979), **51**, 427-431

Should Recurrent Calcium Oxalate Stone formers become Vegetarians?

W. G. ROBERTSON, M. PEACOCK, P. J. HEYBURN, F. A. HANES, A. RUTHERFORD, E. CLEMENTSON, R. SWAMINATHAN and P. B. CLARK

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Summary—The hypothesis that the incidence of calcium stone disease is related to the consumption of animal protein has been examined. Within the male population, recurrent idiopathic stone formers consumed more animal protein than did normal subjects. Single stone formers had animal protein intakes intermediate between those of normal men and those of recurrent stone formers.

A high animal protein intake caused a significant increase in the urinary excretion of calcium, oxalate and uric acid, 3 of the 6 main urinary risk factors for calcium stone formation. The overall relative probability of forming stones, calculated from the combination of the 6 main urinary risk factors, was markedly increased by a high animal protein diet.

Conversely, a low animal protein intake, such as taken by vegetarians, was associated with a low excretion of calcium, oxalate and uric acid and a low relative probability of forming stones.

It has been suggested that calcium oxalate stone formation in the upper urinary tract is essentially a disease of the more affluent or industrially-developed societies (Andersen, 1973; Blacklock, 1976). This hypothesis is supported by the observation that the rate of hospitalisation for stones in the population has been increasing in the Western world during the last 30 years (Andersen, 1973; Sierakowski *et al.*, 1978; Robertson *et al.*, 1979a). Moreover, there is a strong correlation between the occurrence of stones in a given population or section of society and the level of affluence, as defined both by the mean annual salary and by the expenditure on food in that population (Robertson *et al.*, 1978b).

Preliminary investigations have shown that the only dietary factor which is correlated consistently at all demographic levels with expenditure on food and the occurrence of stones is the intake of animal protein. Conversely, in populations with a relatively high intake of vegetable protein compared with animal protein there is apparently a low incidence of upper urinary tract stones (Robertson *et al.*, 1978b, 1979a). These observations suggest that the risk of stones in a given population is related to the consumption of animal protein.

The object of this paper was to investigate the biochemical changes produced by increasing or decreasing the dietary intake of animal protein and to assess the effect of these changes on the calculated risk of stone formation.

Patients and Methods

In the first part of the study, diet histories on a "free diet" were taken from a total of 85 male, idiopathic stone formers who had formed calcium oxalate-containing stones. Sixty had a history of recurrent stones and 25 had formed only one stone. Diet histories were also taken from 22 normal, male laboratory and medical staff. The diets were analysed for their protein content. Total protein was divided into animal protein (from meat, fish, poultry, eggs and milk products) and vegetable protein. Animal protein was further subdivided into flesh protein (from meat, fish and poultry) and dairy protein (from eggs and milk products).

In the second part of the study, 6 normal male volunteers were studied under home conditions for 12 days during which time they were given dietary advice on maintaining a constant intake

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Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

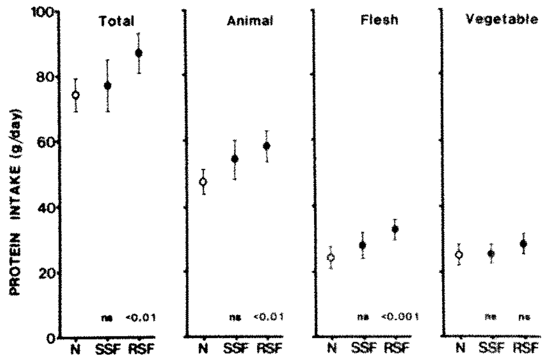

Fig. 1 The mean ±2 SEM dietary intakes of total protein, animal protein, flesh protein and vegetable protein in normal males (N), single calcium stone formers (SSF) and recurrent calcium stone formers (RSF).

of calcium, protein and fluid. On the first 3 days of the study the volunteers consumed about 55 g/day of animal protein. From the fourth to the twelfth day inclusive they ingested an extra 34 g/day of animal protein in the form of tuna fish. Twenty-four-hour urines were collected with preservative on each day and analysed for the 6 main risk factors for calcium stone formation, namely volume, pH, calcium, oxalate, uric acid and the glycosaminoglycan (or acid mucopolysaccharide) inhibitors of calcium oxalate crystallisation, and the overall probability of forming stones calculated (Robertson *et al.*, 1978a).

In the third part of the study 14 normal volunteers (10 males and 4 females) were studied on a high (92 g/day), normal (48 g/day) and low (1 g/day) animal protein intake, for 4 days on each regimen. Calcium and phosphorus intakes were kept constant throughout the study with supplements given in tablet form. On each day, 24-h urines were collected and analysed as described above for the 6 risk factors and from these the overall relative probability of forming stones calculated.

In the final part of the study 24-h urines were collected from a group of 22 vegetarian subjects (10 male and 12 female) and analysed for the 6 risk factors and the overall relative probability of forming stones.

Results

The mean (±2 SEM) dietary intakes of total, animal, flesh and vegetable protein in normal volunteers and stone formers are shown in Figure 1. The recurrent stone formers had significantly higher intakes of total protein than normal individuals and this was almost entirely attributable to a higher intake of animal protein, particularly flesh protein, of about 10 g/day. The single stone formers had values intermediate between those of the normal volunteers and those of the recurrent stone formers.

Figures 2a and 2b show the effect on urine

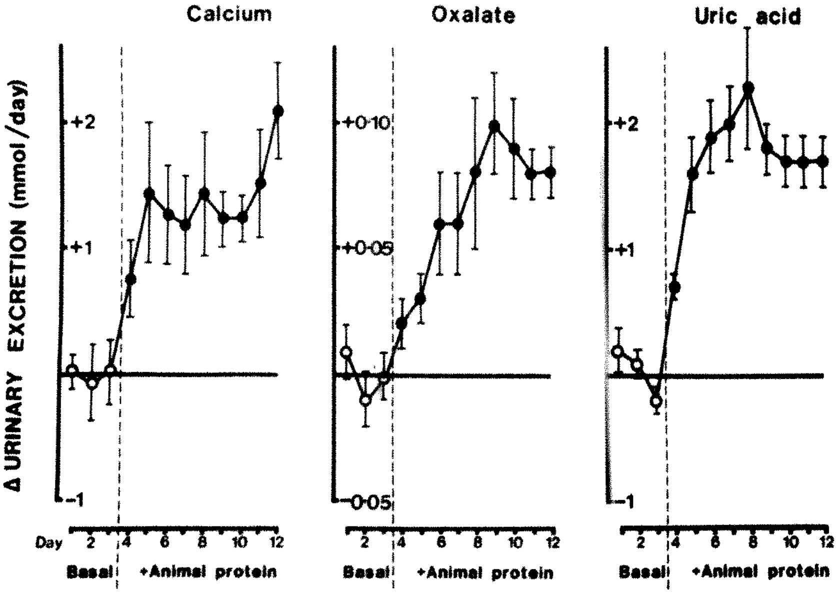

Fig. 2a The mean ±SEM changes from the basal diet in the urinary excretions of calcium, oxalate and uric acid.

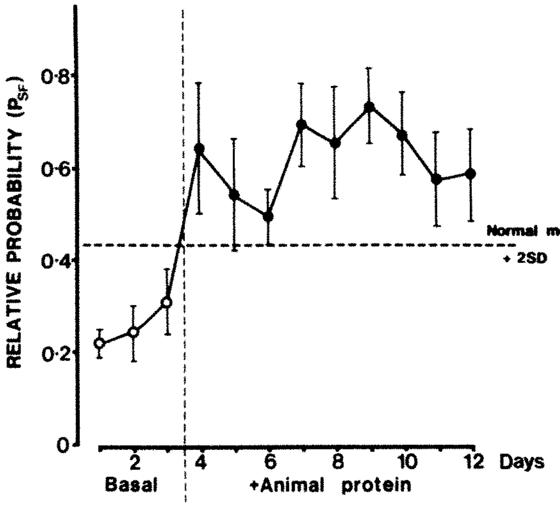

Fig. 2b The mean ±SEM relative probability of forming stones (P_{SF}) during the basal diet and the period of high animal protein intake.

composition and the calculated risk of stones (mean±SEM) of increasing the dietary intake of animal protein by 34 g/day in a group of 6 normal male volunteers. During the period of high animal protein intake there were significant increases in urinary calcium (23%), oxalate (24%) and uric acid (48%). The overall effect of these changes was to increase the mean relative probability of forming stones by about 250%, most of the values exceeding the upper limit of normal.

Figure 3 shows the effect on urine composition and the calculated risk of stones of decreasing animal protein intake from a high intake (92 g/day), through a normal intake (48 g/day) to a very low intake (1 g/day). The mean (±2 SEM) values for urinary calcium, oxalate and uric acid and the relative probability of forming stones fell significantly during each stage of the study.

Figure 4 shows the urine composition and calculated risk of stones in vegetarian subjects as compared with normal subjects and stone formers (taken from the data of Robertson *et al.* (1978a)). The mean (±2 SEM) values of urinary calcium, oxalate and uric acid and the overall relative probability of forming stones were considerably lower in the vegetarian group than among normal and stone forming meat-eating individuals.

Discussion

It has become clear from various epidemiological studies that, at several demographic levels, the incidence of urinary stone disease is related to the level of affluence in the population (Andersen, 1973; Robertson *et al.*, 1978b, 1979a). The only dietary factor which is consistently correlated with affluence and the incidence of stones is the intake of animal protein (Robertson *et al.*, 1978b, 1979a). This study confirms that idiopathic calcium stone formers do, in fact, consume more animal protein, particularly that derived from meat, fish and poultry, than do normal subjects and that this accounts to a large extent for their higher calcium, oxalate and uric acid excretion and

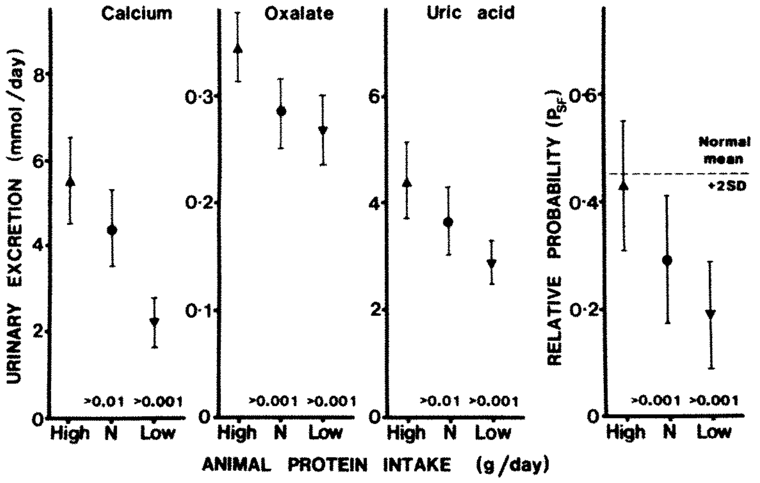

Fig. 3 The effect of reducing the consumption of animal protein from a high (92 g/day) through a normal (N) (48 g/day) to a low (1 g/day) intake on the urinary excretions of calcium, oxalate and uric acid and the relative probability of forming stones (P_{SF}).

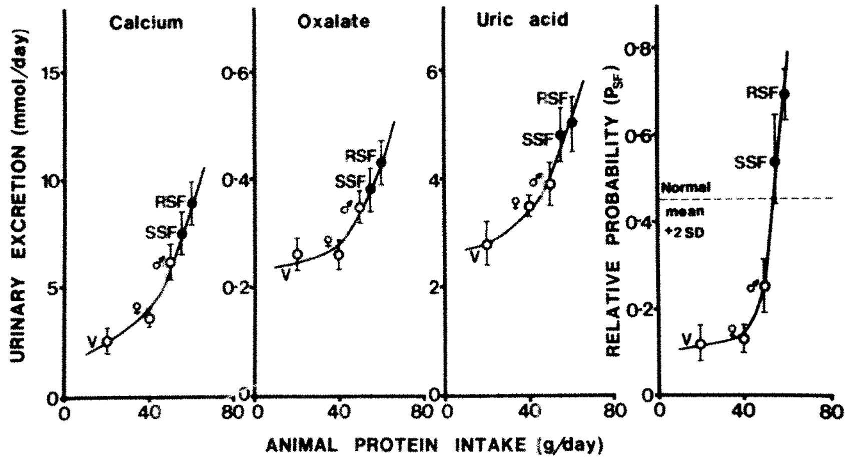

Fig. 4 The mean ±2 SEM values for the urinary excretion of calcium, oxalate and uric acid and the relative probability of forming stones (P_{SF}) in relation to the mean dietary intake of animal protein in vegetarians (V), normal females (♀), normal males (♂) single stone formers (SSF) and recurrent stone formers (RSF).

increased risk of stones. The higher the intake of animal protein, the more likely is the individual to have multiple stones than a single stone episode.

Biochemically, the effect of a diet high in animal protein is to increase the urinary excretion of calcium, oxalate and uric acid. Present theories attribute the increase in urinary calcium to increased bone resorption (Linkswiler *et al.*, 1974; Chu *et al.*, 1975; Adams *et al.*, 1978), the increase in urinary oxalate to increased metabolism of phenylalanine, tyrosine and tryptophan (Robertson *et al.*, 1979b), all of which are present in higher proportions in animal protein than in vegetable protein (Paul and Southgate, 1978), and the increase in uric acid excretion to the additional purine nitrogen accompanying most flesh protein (Coe *et al.*, 1976). Thus 3 out of the 6 main urinary risk factors for calcium stone formation are affected adversely by a high intake of animal protein. It is perhaps not surprising, therefore, that there is a strong relationship between the incidence of stones and the level of consumption of animal protein in the population.

Conversely, a diet low in animal protein reduces the urinary excretions of the 3 risk factors so that the overall probability of forming stones becomes very low indeed. This may explain the apparently low incidence of stones in vegetarian societies. We are currently investigating this relationship in the UK by studying the incidence of stones among vegetarians in a nationwide survey carried out under the auspices of the Vegetarian Society.

Figure 3 shows clearly that normal subjects put on a low animal protein diet respond by producing urine with a low predicted risk of stone formation. If stone formers can be shown to respond in the same way as normal individuals, it may be worthwhile advocating a more vegetarian form of diet as a means of reducing the risk of stone recurrence. Indeed, inflation—by reducing the purchase and consumption of animal protein—appears to be achieving this goal already, since the annual hospitalisation rate for stone disease in the UK has been falling in recent years (Robertson *et al.*, 1979a; Peacock *et al.*, 1979).

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Maximum Urinary Concentration Ability in Patients with Idiopathic Hydronephrosis

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Summary—The maximum urinary concentration ability and renal parenchymal function of each kidney were investigated in 34 patients with unilateral hydronephrosis. The ability to concentrate urine was not reduced in 10 hydronephrotic and 24 contralateral kidneys. The concentration ability was moderately reduced in 14 hydronephrotic and 10 non-hydronephrotic kidneys and severely impaired in 10 hydronephrotic kidneys. A reduced concentration ability was found almost entirely in hydronephrosis complicated with upper urinary tract infection or renal calculi. Hydronephrotic kidneys without these complications showed a normal concentration ability in 10 of 11 cases.

Parenchymal function was reduced in only 10 hydronephrotic kidneys, 7 of which had had upper urinary tract infections and 3 of which had renal stones.

It is our opinion that uncomplicated cases of unilateral hydronephrosis should not be operated upon unless necessitated by signs and symptoms. Measurement of the maximum urinary concentration ability might be helpful in setting the correct indication for surgery in borderline cases.

Patients with unilateral hydronephrosis due to pelviureteric junction obstruction often have no reduction of their renal parenchymal function, as measured by clearance and renographic techniques (Bratt *et al.*, 1977). Total as well as divided renal functions were found to be within normal limits in 27 of 50 patients with unilateral hydronephrosis, *i.e.* the glomerular and proximal tubular functions were not reduced in half of the patients afflicted by this disease. It is reasonable to assume, however, that during the development of hydronephrosis in these patients, obstruction to urine flow might influence the distal tubular function at an earlier stage than that of the proximal part of the nephron.

A sensitive method to evaluate the function of the distal part of the tubules and the collecting ducts is measurement of the maximum urinary concentration ability. A concentration test, using pitressin tannate in oil, has been used for this purpose (Jones and de Wardener, 1956; de Wardener, 1956). Desmopressin (desamino-d-arginin-vasopressin, DDAVP), which is an analogue of the antidiuretic hormone used for treating diabetes insipidus, has replaced the use of pitressin tannate (Delin *et al.*, 1978). This has made the use of the concentration test much more practical, as maximum urinary concentration can be achieved within a few hours. We took advantage of this improvement to study the concentration ability of the 2 kidneys in patients with unilateral hydronephrosis due to pelviureteric junction obstruction, and to relate the maximum urinary concentration to the renal parenchymal function.

Patients and Methods

The study comprises 34 patients: 15 men, mean age 38 years (range 24-57) and 19 women, mean age 30 years (range 22-63) with unilateral hydronephrosis due to pelviureteric junction obstruction. The dominating symptoms initiating the investigations were lumbar pain and/or episodes of acute upper urinary tract infection. Patients with upper urinary tract infections were examined at least 6 months after the last episode (15 patients). Renal stones were observed in 8 patients, 2 of whom also had had an acute upper urinary tract infection. Only 2 patients had hypertension. Both were on treatment with thiazides and hydralazine.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

One of these patients also had a renal stone in the hydronephrotic kidney; the other had no signs of complicating disorders. Thus a total of 11 patients had no signs of complicating disorders such as upper urinary tract infection or renal stones.

The diagnosis of hydronephrosis was established from routine intravenous urography. The findings of wide renal pelves and calices, high insertion of the ureter on the renal pelvis, and a ureter of normal size below the pelviureteric junction were the significant signs. The significance of the hydronephrosis was estimated from the findings of an abnormal drainage function on isotope renography and distension of the calices on diuretic urography (Bratt *et al.*, 1978).

Routine blood and urine analyses, intravenous urography, renal angiography, diuretic urography, isotope renography and the measurement of glomerular filtration rate were performed in all patients. Intravenous urography and renal angiography were performed by standard techniques and diuretic urography after loading by infusion of mannitol (Bratt *et al.*, 1978).

Isotope renography was performed using our previously described equipment and technique (Aurell *et al.*, 1971).

The renal parenchymal function of each kidney was determined from the uptake ratio given by readings of the isotope renography curve during the first 2 minutes of recording. Based on data previously published by Aurell *et al.* (1971), the following criteria were applied: normal function = ratio > 1.4; moderately decreased function = ratio 1.2 to 1.4; severely decreased function = ratio < 1.2. The correlation between the uptake ratio and inulin clearance had previously been established (Aurell *et al.*, 1971; Bratt *et al.*, 1977).

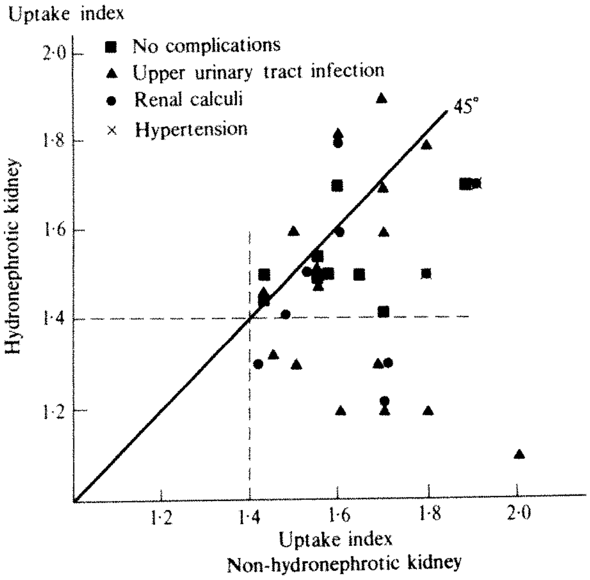

Fig. 1 Renal parenchymal function estimated from renography in 34 patients with unilateral hydronephrosis. The broken lines indicate the border between a reduced and a non-reduced function (up-take ratio = 1.4).

The glomerular filtration rate was measured using the single injection technique utilising the ^{51}Cr-EDTA complex as filtration marker (Bröchner-Mortensen, 1972).

The maximum urinary concentration was achieved by intranasal application of 40 μg desmopressin (Minirin$^{(R)}$: Ferring, Sweden) after 12 h of fluid restriction. One hour later, a retrograde ureteric catheter was introduced into the renal pelvis of the hydronephrotic kidney, which was drained. The urine from the contralateral kidney was sampled from an indwelling Foley catheter in the bladder. Urine samples were simultaneously collected from the pelvic and the bladder catheters, 2 and 4 h after the catheters had been placed in position. The correct position of the ureter catheter in the renal pelvis and the absence of leakage along the catheter were checked by fluoroscopy at the end of the investigation.

The urinary osmolality was measured using a Knauer's osmometer. The following criteria were applied:

Normal concentrating ability = > 800 mOsm/kg H_2O
Moderately decreased ability = 500-800 mOsm/kg H_2O
Severely decreased ability = < 500 mOsm/kg H_2O

Results

The total glomerular filtration rate was normal or close to normal in all patients. The mean value was 94 ± 8 ml/min/1.73 BSA. The renal parenchymal function of the hydronephrotic kidneys and the non-hydronephrotic contralateral kidneys in each patient was evaluated from renography (Fig. 1). The parenchymal function of the hydronephrotic kidneys was moderately or severely reduced in 10 patients, as shown by the uptake ratio < 1.4; 7 of these patients suffered from upper urinary tract infection and 3 patients had renal stones on the hydronephrotic side. The

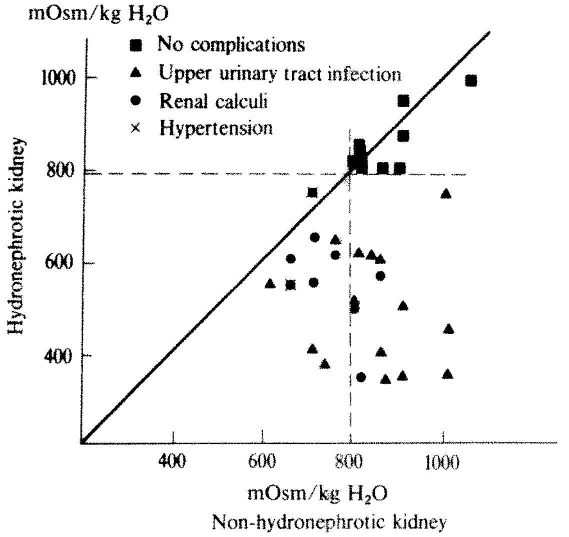

Fig. 2 Maximum urinary concentration ability in 34 patients with unilateral hydronephrosis. The broken lines indicate the border between a normal concentration ability and a decreased concentration ability (800 mOsm/kg H_2O).

remaining 24 hydronephrotic kidneys and all contralateral kidneys had a normal parenchymal function with an uptake ratio of >1.4.

The maximum concentration ability of the hydronephrotic kidneys and contralateral kidneys is shown in Figure 2. The concentration ability was normal (>800 mOsm/kg H_2O) in 10 hydronephrotic and 24 contralateral kidneys and moderately decreased in 14 hydronephrotic and 10 contralateral kidneys. A severely decreased concentration ability was present in 10 hydronephrotic kidneys, but never in the contralateral kidneys. The maximum concentration ability of the hydronephrotic kidneys is given in the table, which shows that hydronephrotic kidneys complicated with upper urinary tract infection or stones had a moderately to severely reduced concentration ability. Furthermore, hydronephrotic kidneys without these complications had a normal maximum concentration ability in 10 of 11 cases.

Reduced parenchymal function was present in 10 hydronephrotic kidneys. In all of these specimens a reduced maximum concentration ability was observed. The concentration ability was moderately decreased in 7 patients and severely decreased in 3; all 10 of them had had upper urinary tract infections. In the remaining 24 cases of hydronephrosis where no reduction in parenchymal function was observed, a decreased urinary concentration ability was found only in patients with upper urinary tract infections, renal stones and in a single case of hypertension.

Table Concentration Ability in Patients With Unilateral Hydronephrosis

Concentration ability	*N*	*Patients with*		
		No complications	*Upper urinary tract infections*	*Renal stones*
Normal (>800 mOsm/kg H_2O)	10	10	0	0
Moderately decreased (500-800 mOsm/kg H_2O)	14	1	7	6
Severely decreased (<500 mOsm/kg H_2O)	10	0	8	2

Discussion

The diagnosis of hydronephrosis is readily made from routine intravenous urography, but an assessment of the significance of pelvic enlargement is much more difficult to establish. We have recently recommended more use of both isotope renography and diuretic urography for this purpose (Bratt *et al.*, 1978). Using such measures, it is obvious that quite a large proportion (approximately 50%) of patients with unilateral hydronephrosis due to obstruction at the pelviureteric junction have an intact renal parenchymal function. This is now also shown to be valid for the maximum concentration ability.

The patients included in this study would all have been considered for surgery according to previous criteria. They presented with a history of lumbar pain and intravenous urography showed wide caliceal and renal pelvic systems and a high insertion on the renal pelvis of a ureter of standard diameter. Furthermore, the hydronephrotic kidney had abnormal drainage as shown by renography and diuretic urography.

The indication for surgery in hydronephrotic kidneys is often based on the assumption that hydronephrosis is a threat to renal function. Obviously, patients with a normal renal function would not benefit from surgery in this respect. In a previous study, we followed a group of 12 patients with uncomplicated unilateral hydronephrosis for 3 to 5 years without noting any complications or reduction in the glomerular filtration rate except for one individual who developed a renal stone. It is, therefore, crucial to identify those patients who would otherwise be subjected to an unnecessary operation.

The desmopressin test used in this study has been used as an alternative to the classic pitressin test to measure the maximum urinary concentration. The desmopressin test has the particular advantages of making it possible to evaluate the maximum concentration ability within a few hours without much discomfort to the patient (Delin *et al.*, 1978). We used this test with catheterisation of the ureters and no side effects were observed in the patient study.

It is clear from the present study that patients who presented with complications also had signs of a damaged concentration ability. Patients without complications, on the other hand, were far better off. In fact, no patient had a reduced concentration ability in this group. However, quite a few patients had a reduced concentration ability in both kidneys (Fig. 2). These individuals had bilateral disease and the reduced function or the development of renal stones in these patients could hardly be related to unilateral hydronephrosis. On the other hand, in those patients with reduced renal function on the hydronephrotic side but with normal contralateral function, it seems possible that the hydronephrosis might have promoted the development of renal stone, and/or an upper urinary tract infection may have damaged the kidney. It is reasonable to expect that a successful operation in hydronephrosis complicated by stone or upper urinary tract infection would reduce the risk for further complications.

It is generally accepted that functional abnormalities are present in all obstructed kidneys. Evidence from clinical (Zetterström *et al.*, 1958; Berlyne, 1961; Platts and Williams, 1963) and experimental (Chisholm, 1964, 1970) studies suggests that the reduced function is present in all subjects even after the relief of obstruction.

Chisholm (1964) found from experimental studies on dogs that recovery after uncomplicated obstruction varied directly with the duration of obstruction. Chisholm (1970) also pointed out that "it is often difficult to determine how much a failure to recover may be due to pyelonephritis even when the urine is sterile". As shown by Bratt *et al.* (1977), a successful operation may restore the renal function. In the absence of complicating infection Zetterström *et al.* (1958), studying 2 children with a post-operative pyelostomy and reduced maximum concentration ability after pitressin tannate administration, reached the conclusion that the renal damage was probably caused by increased intrapelvic pressure, as did Campell (1970). However, the basal intrapelvic pressure measured in the human hydronephrotic kidney is generally not increased (Struthers, 1969) and was on average 5.2 cm H_2O (range 1.3-10.0 cm H_2O) (Bratt *et al.*, 1979). The administration of osmotic diuretics, however, usually results in increased pelvic pressure (mean 71 cm H_2O, range 10.0-137.5 cm H_2O) (Bratt *et al.*, 1979).

In the present study we have shown that, in the absence of complicating disorders and in the presence of normal parenchymal renal function, distal tubular function is intact in patients with unilateral hydronephrosis. The observation of normal concentration ability, especially if both sides have the same value, clearly indicates a well preserved renal function. Thus we have defined a group of patients in whom a conservative approach to treatment could be applied. The use of the desmopressin test is recommended in the preoperative evaluation of borderline cases.

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Intravenous Inosine for Ischaemic Renal Surgery

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Summary—The use of the intravenously administered nucleotide inosine is described for the protection of function in the human kidney undergoing ischaemic renal surgery. The treatment of 7 patients is described. The simplicity of the technique is emphasised.

Protection of renal function by the intra-arterial injection of the nucleotide inosine has been well documented (Fernando *et al.*, 1976, 1977a, 1977b). Its successful use for functional preservation of human kidneys during ischaemic renal surgery has also been reported (Wickham *et al.*, 1978a, b). Our previous studies on the rat kidney have also demonstrated that inosine, whether administered intra-arterially to the kidney or intravenously or intraperitoneally to the whole animal, is equally effective in preserving renal viability. It therefore seemed logical to evaluate the effect of intravenously administered inosine in the clinical situation.

In this study we report on the use of intravenously administered inosine in 7 patients undergoing ischaemic renal surgery.

Patients and Methods

Seven patients were treated. Six patients had staghorn calculi and one patient had an adenocarcinoma in a solitary kidney. Of the 6 patients with staghorn calculi, 2 had solitary kidneys: all patients had pre-operative estimations of serum creatinine. Four patients had pre-operative differential I_{123} gamma camera renography.

At operation the kidneys were exposed through either a twelfth rib loin incision or a modified lumbotomy. The kidneys were all fully mobilised and the renal artery dissected cleanly preparatory to clamping. Ten minutes prior to clamping 2 g of inosine in 80 ml of diluent as Trophycardyl (Laboratories Innothera, 94110 Arcueil, France) were administered intravenously. The renal artery was then occluded with a light bulldog clamp and appropriate intrarenal surgery carried out. At the conclusion of the procedure a 12 FG Porges nephrostomy tube was inserted and the wound closed in layers with drainage.

Table 1 Patients Treated with Intravenous Inosine

		Ischaemia time (min)
M.S.	Tumour in solitary kidney	55
A.J.	Staghorn in solitary kidney	57
M.H.	Staghorn in solitary kidney	60
*D.L.	Staghorn in left kidney	38
*C.S.	Staghorn in left kidney	45
*T.K.	Staghorn in left kidney	90
*U.W.	Staghorn in left kidney	65

*Contralateral kidney normal.

Serum creatinine was measured at 24 h, 7 days and at approximately 30 days after operation.

In 4 patients differential renography was performed at approximately the same time intervals after surgery as the creatinine measurements. The ischaemic times, the type of lesion treated and the status of the kidneys are shown in Table 1.

Results

1. General

All patients tolerated the operation satisfactorily. No significant cardiodynamic disturbance was observed in any patient apart from one who exhibited a mild sinus tachycardia for a few hours after operation but was known to have intermittently suffered from this condition before operation.

2. Serum Creatinine Levels

In all patients serum creatinine levels were slightly elevated on the day after operation (Table 2, Fig. 1). These had all returned to pre-operative levels within one month of operation.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

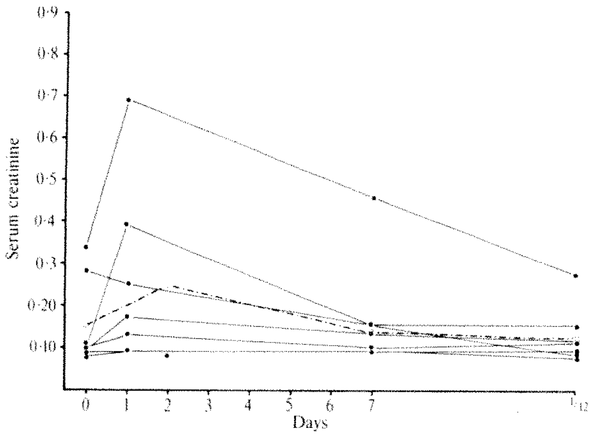

Fig. 1 Serum creatine levels following renal ischaemia and I.V. Inosine protection.

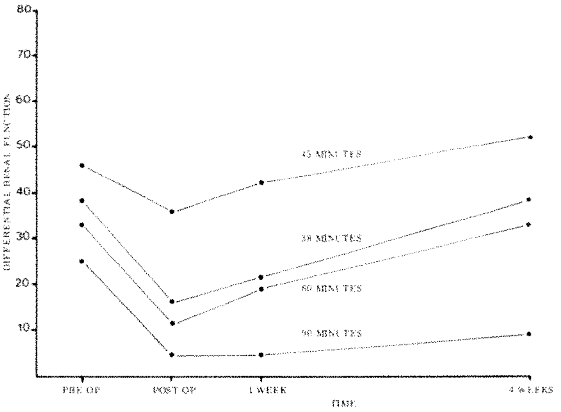

Fig. 2 Per cent differential renal function (renogram) with time following renal ischaemia and I.V. Inosine protection.

3. Differential Renography

In the 4 patients where differential renography was available (Fig. 2), all showed evidence of diminished renographic performance immediately after operation. By one month all but one patient had regained their pre-operative renographic function.

Discussion

These results confirm the protective effect of inosine on renal function during prolonged ischaemia. They also substantiate our previous findings in the rat that the intravenous administration of the nucleotide is as effective in this respect as intra-arterial perfusion. Previous laboratory studies with isotopically labelled inosine have demonstrated that the nucleotide is rapidly taken up from the general circulation into the renal tissue (Fernando *et al.*, 1976) where it is presumed to exert its effect in replenishing the adenylic nucleotide pool.

Table 2 Serum Creatinine Levels (mmol/l) Before and After Operation

		Post-operative (days)			
Patient	*Pre-op*	*1*	*7*	*30*	*Ischaemia Time (min)*
M.S.	0.10	0.39	0.15	0.09	55
A.J.	0.34	0.69	0.46	0.27	57
M.H.	0.08	0.09	0.08	0.08	60
D.L.	0.11	0.17	0.13	0.12	38
C.S.	0.09	0.09	0.09	0.09	45
T.K.	0.10	0.13	0.10	0.13	90
U.W.	0.28	0.25	0.15	0.15	65

The slight depression of renal function as determined by serum creatinine observation and the return to normal levels within a few days after operation are entirely comparable to those observed during regional hypothermic preservation.

Attention must, however, be drawn to the significant depression of renographic function in one patient. Here, due to difficulties during the operation, the ischaemic time was prolonged to 90 min. Serum creatinine was unaffected because the patient had a normal contralateral kidney. Although starting function was only 25% on differential renography, at one month function is still less than half of the pre-operative level, although ultimate improvement may yet occur. This would support our previous observation that protection of function up to one hour of ischaemia is safe. This is particularly well demonstrated in the case of 3 patients with solitary kidneys. Here there is no possible chance that renal function could have been supported by a contralateral normal kidney and the treated kidney has supported the patient throughout. Extension of clamping beyond a period of one hour would seem inadvisable unless sequential hypothermia is utilised.

Analysis of our personal series of 250 cases of ischaemic renal surgery for stone reveals an average ischaemia time of 58 min, so that inosine protection alone would be adequate for the majority of patients undergoing this type of surgery.

The simplicity of this method of preservation of function is extremely attractive. Hypothermic preservation necessarily requires additional equipment and interference within the operative field. Intra-arterial inosine perfusion, whilst reasonably simple, carries with it the possibility of producing endothelial vascular damage with subsequent arterial thrombosis. This applies irrespective of whether the artery is cannulated with a Schwann Ganz Catheter (Marberger and Georgi, 1975) or is directly needled (Wickham *et al.*, 1978a, b). Intravenous administration of the nucleotide is manifestly simple, it allows a clear operative field and causes no danger to the renal artery.

We would advocate the use of intravenous inosine as the method of choice for preservation of renal function for human kidneys undergoing ischaemic operations of not more than one hour's duration.

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Technique of Clearance (or Disconnection) of Dilated Lymphatics in the Renal Hilum and Lower Ureter and Bladder in Cases of Intractable Chyluria or Haemochyluria

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Summary—The indications, investigations and techniques for treating patients with chyluria are presented. Thirty-eight patients were treated by lymphatic disconnection either at renal hilum or at lower ureter and bladder level. Pedal lymphangiography was essential to decide upon the level of operation. Results were satisfactory in the majority when chyluria was intractable.

In India chyluria and haemochyluria are features of filarial infestation. In about 20% of cases the disease takes a relentless course. Patients lose a considerable amount of weight and suffer from intermittent retention due to chylous or haemochylous clots. These patients can be treated by the lymphatic disconnection technique. At many centres this operation is undertaken only at the renal hilum after cystoscopy to detect the side of the greater leak and a retrograde pyelogram to demonstrate the exaggerated pyelolymphatic backflow. At times this operation fails since the exact site of the leak has not been determined. We have been using pedal lymphangiography to determine the exact site of the leak and then to decide on the approach for surgery.

Patients and Methods

Thirty-eight patients with intractable chyluria or haemochyluria were treated by the lymphatic disconnection technique. Thirty of them had leaks around the renal hilum, while the rest had leaks around the lower ureter and the bladder; in 2 cases the cord lymphatics were grossly dilated.

Lymphangiography

The 8 lower tract lesions would have been missed if pedal lymphangiography had not been done (Table). Lymphangiography was indicated when the patient had not responded to prolonged treatment with antifilarial drugs and urinary antiseptics, had lost weight from loss of protein and fat in the urine, or had repeated episodes of urinary infection or clot retention due to haemochylous clots.

Table Site of Chylous Leak

Total number of patients with chyluria	38
Leak around renal hilum	30
Leak around lower ureter and bladder and 2 with dilatation of the spermatic cord lymphatics	8

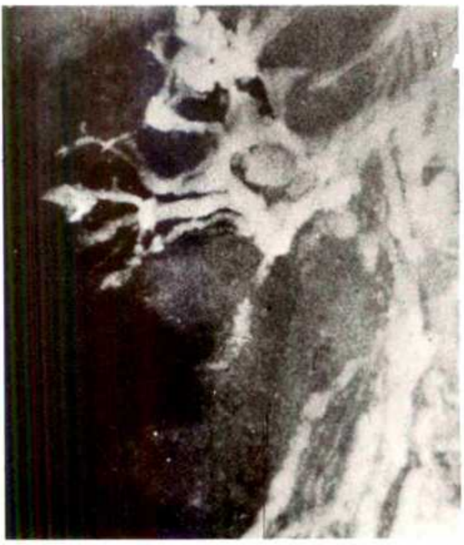

Fig. 1 Varicose lymphatics in the right renal hilum demonstrated by pre-operative lymphangiography.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

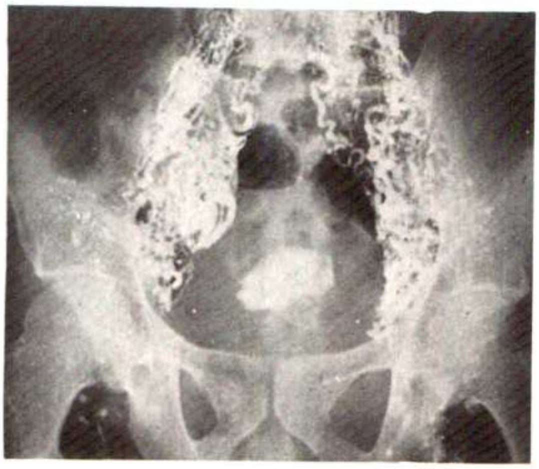

Fig. 2 Dilated lymphatics overlying the iliac vessels producing ethiodol cystogram.

Usually, the lymph varices around the renal vein and artery were responsible for the leak of lymph into the urinary tract, but if the lymphatic varices were predominantly around the lower ureter and bladder, this area might need a separate clearance through a separate incision in the iliac region.

Lymphangiography was done through cannulated lymphatics in the dorsum of the foot, or in some cases of grossly dilated lymphatics of the inguinal region or in the spermatic cord by exposure and direct injection. The lymphangiogram demonstrated the leak convincingly by outlining the caliceal lymphatics and also the grossly dilated lymphatics around the renal hilum (*i.e.* around the renal vein and artery) (Fig. 1); this could be demonstrated at operation by pre-operative injection of these lymphatics with patent blue violet. The same was true in cases where the lymphatics around the lower ureters and bladder were to be cleared (Fig. 2). These lymphatics lay over the iliac vessels and after adequate clearance the iliac vein and artery were seen bare and clean.

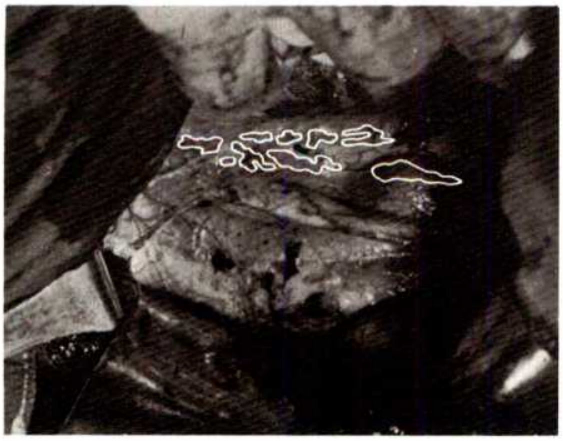

Fig. 3 Dilated lymphatics around the ureter were demonstrated by the blue dye (outlined in white).

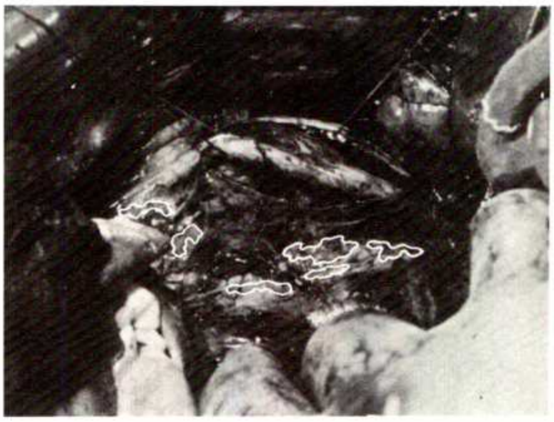

Fig. 4 Part of the lymphatics excised and the ureter retracted to show further lymphatics going up to the renal hilum (outlined in white).

Operative Technique

The pedal lymphatics were cannulated on the side to be operated about an hour before the start of the operation; injection of blue dye was started and continued till the area of clearance was exposed and the abnormal (dilated) lymphatics well demonstrated (Figs. 3, 4 and 5).

It was important to secure or seal off even the tiniest blood vessels and keep the field from getting stained with blood so that the lymphatics could be clearly demonstrated. The dilated lymphatics overlying the ureter and the spermatic or ovarian vessels could be followed right into the renal hilum around the renal vein and artery. The lymphatics were easily isolated, tied and sectioned and some of the varicosities excised, leaving the vein and artery looking bare and clean at the end of the dissection (Fig. 6).

The incision was closed, without drains, but post-operative antibiotic cover was given to prevent infection of any small lymph collection.

Results

Twenty-eight of the 38 patients who underwent operation were cured. Twenty-two had leaks around the renal hilum while 6 patients had a leak around the lower ureter and bladder.

In the remaining patients symptomatic relief

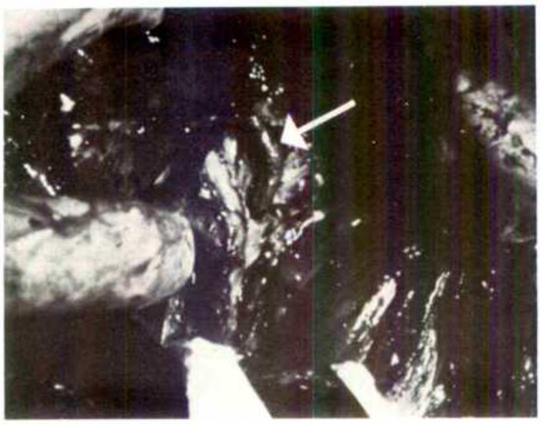

Fig. 5 A large lymphatic entering the renal hilum (arrow). Note that its calibre looks larger than the ureter.

was obtained. They were passing significantly less chyle in their urine and were otherwise in good health

Discussions

Although this condition in the majority of cases responds to treatment with diethyl carbamazine, the refractory ones may require surgical disconnection. This type of management is not expected to lead to a cure but gives long periods of remission in many cases.

The final answer to this problem of filarial chyluria belongs in the domain of the epidemiologist and the public health services, but the surgeon can give relief from distress in some cases.

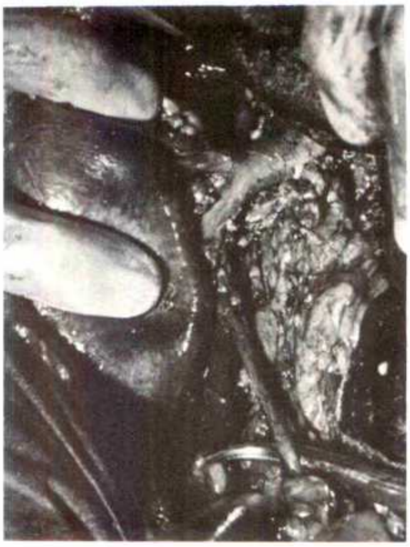

Fig. 6 The renal hilum cleared of varicose lymphatics showing renal vein clean and bare at the end of the operation.

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The Underestimated Hazards of Xanthogranulomatous Pyelonephritis

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Summary—Twenty-eight cases of xanthogranulomatous pyelonephritis were studied in retrospect and difficulties in diagnosis and treatment are described. Awareness of the entity is the most effective safeguard against over-aggressive resection for this benign condition.

A secondary nephrectomy, particularly after pyonephrosis following a calculus, can be one of the most difficult operations in urology, owing to the dense adhesions which surround the kidney. From time to time these cases are made even worse than usual when the surgeon meets tissue which looks vascular and yellow, invades the surrounding tissues, and cuts like invasive carcinoma. Xanthogranulomatous pyelonephritis may mislead one into performing unnecessarily radical surgery, or to abandon the case as being totally inoperable.

Xanthogranulomatous pyelonephritis is a chronic inflammatory granulomatous condition usually seen in kidneys in association with stone. Macroscopically, the granuloma presents a bright yellow appearance and the firm tissue may invade adjacent muscle, diaphragm or bowel.

Microscopically the yellow coloration, which gives it its name, is due to the presence of lipid in the macrophages which compose so much of the inflammatory granulation tissue. It is important to note that these large lipid-containing macrophages can resemble the clear cells of a carcinoma of the kidney. Hence, while the surgeon can be perplexed by the apparently carcinomatous nature of the kidney he is aiming to remove, so also the pathologist may have difficulty, when confronted with a frozen section, in distinguishing between xanthogranuloma and carcinoma.

Patients

Twenty-eight cases were seen at The London Hospital in the last 15 years. There were 10 males and 18 females. Their mean age was 43 years, with a range of 18 to 71 (Fig.). In all cases the diagnosis was confirmed by operation.

Clinical Presentation

Eighty-six per cent of the patients presented with pain in the flank and in 46% this was accompanied by fever and rigors suggestive of inflammatory disease. Twelve patients had clinical evidence of infection in the urinary tract manifested by frequency and painful urination.

In 13 patients there had been a marked loss of weight, accompanied by anorexia in 10. Only 7 patients had haematuria.

Physical Signs and Investigation

In 18 cases there was a large mass in the loin, which was tender in 11. Hypertension was present in 6 patients. Investigations revealed anaemia in 54% of cases and confirmed the presence of urinary infection in 79%. The infection was caused by *Proteus mirabilis* in 11 cases, all of which had large struvite stones.

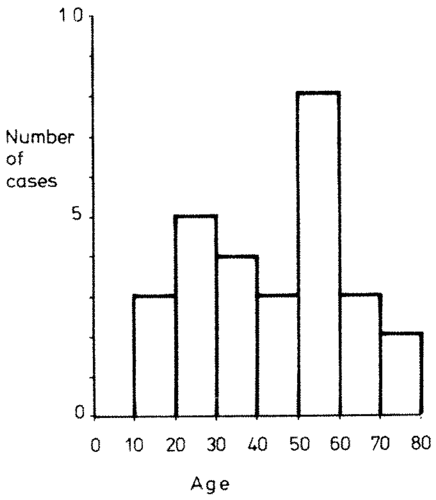

Fig. Age distribution in 28 patients with xanthogranulomatous pyelonephritis.

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Radiological findings were seldom clearcut. The patients fell into 2 main groups: (*a*) those with a non-functioning kidney and an obvious stone (15) and (*b*) those with a non-functioning mass and no stone (9), raising the suspicion of carcinoma.

Treatment

In 27 patients nephrectomy was performed, the one exception having such dense fibrous tissue after several previous operations that he was considered inoperable. His recovery was marked by protracted illness and persistent fistula over a period of months.

The psoas was deeply invaded in 5 cases and in one case the diaphragm and aorta were firmly embedded in the mass. Bowel was involved in 4 cases. In 2, hemicolectomy was performed. In one, part of the wall of the colon was excised and the defect repaired without complication. The fourth underwent intracapsular nephrectomy, leaving the capsule attached to the bowel.

Discussion

Xanthogranuloma, the great imitator, is a pit for the unwary and awareness of the condition remains the most important factor in diagnosis. Symptoms and physical signs with a firm, painful mass in the loin, loss of weight, anaemia, haematuria and a calcified functionless mass on urography strongly suggest a diagnosis of carcinoma. When the kidney retains some function, the radiographic appearances of these kidneys are many and varied. If localised, the disease can produce distortion of the calices and infiltration of the perinephric fat may make the renal outline irregular. When a stone is present, the kidneys are often functionless and this should perhaps raise the suspicion of xanthogranulomatous pyelonephritis. Angiography is said to delineate the extent of the disease (Malek and Elder, 1978) and usually shows an underperfused or avascular mass, but even then will not exclude cancer with certainty. Ultrasound demonstrates a solid lesion and scintiscans show patchy or complete loss of function. Percutaneous renal puncture produces purulent sanguinous material only and cannot exclude carcinoma (Hatch and Cockett, 1964).

So far there has been no opportunity to perform EMI scanning of such a case, but it would seem unlikely that this, or any other pre-operative investigation, will discharge the surgeon of his obligation to explore the kidney.

It is then that surgical difficulty arises. One encounters an unusually hard mass which appears to infiltrate the surrounding tissues of the kidney, giving at first view the impression that this is an inoperable and fixed carcinoma. The tissue is often vividly yellow and even a frozen section may give the surgeon no clear diagnosis. Faced with clinical evidence of upper tract infection, and especially when there is a stone, it is worthwhile remembering the possibility of xanthogranuloma. This may allow a less radical excision of the mass. Nevertheless, an attempt should be made to remove it, even incompletely, for if left *in situ* the natural history of xanthogranuloma is of a protracted and debilitating illness marked by rigors, secondary infection and fistulae for which an even more difficult nephrectomy will usually be required months later.

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Frusemide Intravenous Urography in the Diagnosis of Pelviureteric Junction Obstruction

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Summary—Standard intravenous urography is not a reliable method of demonstrating pelviureteric junction obstruction. Frusemide urography enables 3 groups to be defined on the basis of the percentage increase in the size of the renal pelvis after the diuretic. These groups are clinically significant.

When pelvicaliceal dilatation is demonstrated radiologically it is important to determine whether pelviureteric junction obstruction is the cause. Standard intravenous urography does not reliably differentiate the obstructed from the non-obstructed system. Percutaneous pressure/flow studies may give useful urodynamic information about the pelviureteric junction (Whitaker, 1973; Whitfield *et al.*, 1977). Radioisotope techniques can provide urodynamic data and also demonstrate the effect of obstruction on renal function (Whitfield *et al.*, 1978; Britton *et al.*, 1979).

This study describes a simple technique of frusemide intravenous urography (FIVU) which may be used as a reliable screening test for pelviureteric junction obstruction. The investigation is available to all urologists and requires no specialised equipment. Limits are defined on which it is safe to base clinical management.

Patients and Methods

High dose intravenous urography (650 mg iodine/kg body weight) was performed in the hydrated patient. Forty milligrams of frusemide were given intravenously 20 min after the injection of contrast. Films were taken immediately before and 15 min after the injection of frusemide. The size of the renal pelvis on these films was measured by a technique which has been previously described (Ward *et al.*, 1976), and the percentage increase in size after the diuretic calculated.

Patients were divided into 3 groups: those in whom there was an increase in renal pelvis size of (*a*) more than 22%, (*b*) 10 to 22% and (*c*) less than 10%. Where contrast wash-out was complete after frusemide and the renal pelvis no longer visible for measurement the percentage increase was recorded as nil.

Group I—Operated Cases

Twenty-six kidneys in 25 patients were studied. Four patients had had previous operations for the relief of pelviureteric junction obstruction. Anderson-Hynes pyeloplasty was performed in 25 cases and Culp pyeloplasty in one. Follow-up studies were performed in 24 cases.

Group II—Non-operated Cases

Fifteen kidneys in 13 patients were studied. Four patients had previously undergone renal surgery on the affected side, 2 having had pyeloplasties and 2 having undergone surgery for staghorn calculi. Follow-up studies have been performed in 6 cases.

Results

Group I—Operated Cases (26)

(1) Pre-operative Studies The increase in the size of the renal pelvis after frusemide varied between nil and 106% (mean 51%). In one patient with poor renal function, insufficient definition prevented measurement.

The results of gamma camera renography and pressure/flow studies in patients in this group are shown in Tables 1, 2 and 3.

(2) Post-operative Studies (Fig. 1) In the 24 cases who had follow-up FIVU the increase in the size of the renal pelvis varied between nil and 33% (mean 9%). Insufficient definition of the

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Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 1 Results of Pre-operative Renography and Pressure/Flow Studies in Operated Patients with an Increase in Pelvis Size of more than 22% after Frusemide

	Obstructed	*Unobstructed*	*Equivocal*	*Failed Test*	*Not done*
Renography	10	5	1	2	0
Pressure/Flow	8	1	0	3	6

collecting system in the same one patient made measurement impossible.

The results of post-operative gamma camera renography are shown in Table 4.

Group II—Non-operated Cases (15)

(1) Initial Studies The increase in the size of the renal pelvis varied between nil and 37% (mean 10%). In one patient with very poor function in a solitary kidney, insufficient definition after contrast made measurement impossible.

The results of gamma camera renography and pressure/flow studies are shown in Table 5.

(2) Follow-up Studies (Fig. 2) Six patients had follow-up FIVUs. The increase in renal pelvis size after frusemide varied between 4.9 and 80% (mean 25%).

The results of gamma camera renography in this group are shown in Table 6.

Comparison of FIVU with Standard IVU (Table 7)

Of the 41 cases included in the study, 19 in the operated group and 11 in the non-operated group had had standard IVUs performed before being referred to the Department of Urology. The diagnosis which was made radiologically on the basis of these standard IVUs was compared with

Table 2 Results of Pre-operative Renography and Pressure/Flow Studies in Operated Patients with an Increase in Pelvis Size of 10 to 22% after Frusemide

	Obstructed	*Unobstructed*	*Not done*
Renography	2	1	0
Pressure/Flow	0	2	1

Table 3 Results of Pre-operative Renography and Pressure/Flow Studies in Operated Patients with an Increase in Pelvis Size of Less than 10% after Frusemide

	Obstructed	*Unobstructed*	*Not done*
Renography	0	4	0
Pressure/Flow	0	2	2

Table 4 Results of Renography Post-operatively in the 3 Urographic Groups

Post-op. increase in pelvis size after frusemide	*No.*	*Renography*	
		Obstructed	*Unobstructed*
<10%	14	0	14
10-22%	5	0	5
>22%	4	2	2

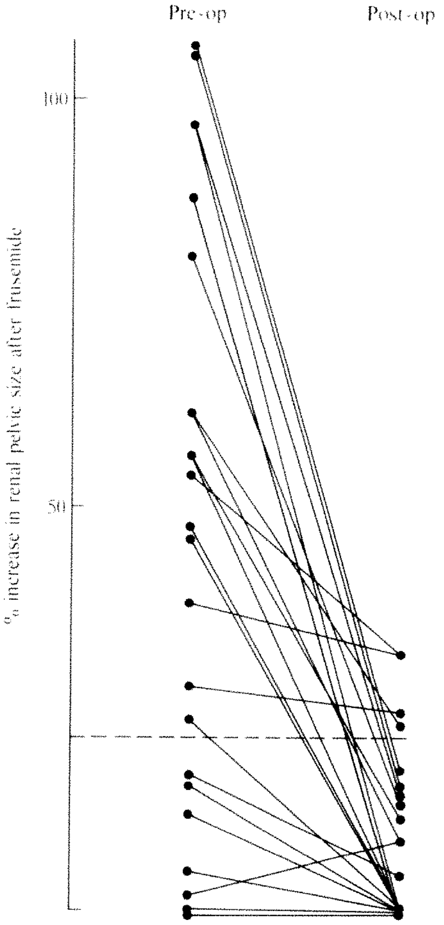

Fig. 1 *Operated Group:* Percentage increase in renal pelvic size after frusemide pre-operatively and post-operatively.

Table 5 Results of Renography and Pressure/Flow Studies in Non-operated Group

Increase in pelvis size after frusemide	*No.*	*Renography*				*Pressure flow*			
		Obstructed	*Unobstructed*	*Equivocal*	*Failed*	*Obstructed*	*Unobstructed*	*Equivocal*	*Not done*
<10%	10	2	6	1	1	0	2	2	6
10-22%	1	1	0	0	0	0	0	0	1
>22%	3	0	3	0	0	0	1	0	2

the diagnosis made on the basis of the pre-operative or initial FIVU.

In 6 cases the FIVU confirmed obstruction and in 3 cases confirmed non-obstruction. In 6 cases the FIVU showed evidence of obstruction not apparent on standard urography and in 5 cases the FIVU showed no evidence of obstruction when a diagnosis of obstruction had been made on standard urography. In 8 cases the standard intravenous urogram was equivocal and FIVU showed obstruction in 4 and no obstruction in 4. In 2 cases standard urography was said to show obstruction and the FIVU was equivocal.

The results of standard urography and the FIVU agreed in 9 out of 30 cases (30%) and disagreed in 11 out of 30 cases (37%). In 8 out of 30 cases (27%) standard urography was equivocal and the diagnosis was made by FIVU. In 2 cases (6%) standard urography was said to show obstruction and FIVU was in the equivocal range (10 to 22%).

Pain

In Group I, the operated group, loin pain was the presenting symptom in 25 out of 26 cases. The 5 patients in whom the *pre-operative* increase in renal pelvis size after frusemide was less than 10% all continued to have pain *post-operatively*. Of the 4 cases who *post-operatively* showed an increase in renal pelvic size after frusemide of more than 22%, 2 continued to have loin pain.

Table 6 Results of Follow-up Renography in Non-operated Group

Increase in pelvis size after frusemide	*Renography*	
	Obstructed	*Unobstructed*
>10%	1	2
10-22%	0	1
<22%	0	2

Table 7 Comparison of Diagnoses Made on Standard IVU and FIVU

	Standard IVU		
	Obstructed	*Unobstructed*	*Equivocal*
FIVU			
Obstructed	6	6	4
Unobstructed	5	3	4
Equivocal	2	0	0

In Group II, the non-operated group, 8 cases presented with loin pain, though only one showed an increase in pelvic size of more than 22% after frusemide. At follow-up all of these patients are asymptomatic; the patient who initially showed

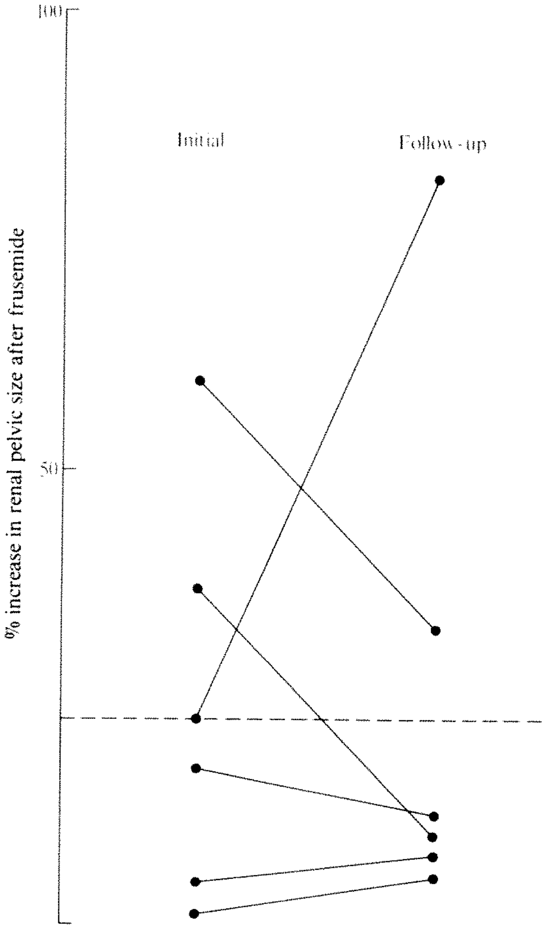

Fig. 2 *Non-operated Group:* Percentage increase in renal pelvic size after frusemide initially and at follow-up.

obstruction on urography is no longer obstructed. Of the remaining 7 cases, 2 showed an increase in pelvic size initially and at follow-up of more than 22% but remain asymptomatic, renographically unobstructed and with unchanged overall and differential renal function.

Discussion

Pelviureteric junction obstruction is not an "all or nothing" but a graded phenomenon. It is unlikely therefore that different methods of investigation will define exactly the same limits of normality and abnormality. We set out to evaluate a test which was easy to perform and on the results of which clinical management could be safely based.

The size of the renal pelvis was measured since it proved difficult to quantify change in caliceal size when calices were overlying the renal pelvis. The percentage increases in renal pelvic size after frusemide have been divided into 3 divisions since an earlier study (Whitfield *et al.*, 1977) suggested that such divisions correlated best with the results of pressure/flow studies and gamma camera renography. These divisions can readily be made by eye without using computer measurements.

There are circumstances when the FIVU is difficult to interpret. In those cases in which previous surgery has caused extensive peripelvic fibrosis, increase in size of the renal pelvis is unlikely to be possible because of rigidity of the pelvic wall. Where renal function is significantly impaired the test cannot be used because of poor definition after injection of contrast.

Apart from the increase in size of the pelvis there are other features of the FIVU which are important and helpful diagnostic guides. For instance, any increase in the size of a calix following frusemide is at least as important as the change in the size of the renal pelvis. This feature is most valuable when there is reason to suspect that the renal pelvis has a low compliance. Contrast dilution after a diuretic cannot be quantified, but a complete wash-out is a reliable sign of a non-obstructed system.

Intravenous urographic investigations need to be tailored to different clinical problems (Turner Warwick *et al.*, 1979). This study shows that standard urography is an unreliable investigation in the diagnosis of obstruction in a dilated pelvicaliceal system. Frusemide urography enables the clinician to differentiate between an obstructed and a non-obstructed system with a degree of accuracy comparable to other methods of investigation. There remains a small equivocal group (15% in this series) in which the decision on whether or not surgery is indicated rests on symptomatology and differential renal function studies. This equivocal group is best investigated in centres in which gamma camera renography is available.

We conclude that standard intravenous urography is unreliable in the diagnosis of pelviureteric junction obstruction. Frusemide intravenous urography is an accurate screening test and will resolve the problem of whether pelviuretic junction obstruction is present in 85% of cases. On the basis of the features that we have described, the FIVU can be safely adopted as the initial investigation of choice.

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Diuresis Renography and the Results of Pyeloplasty for Idiopathic Hydronephrosis

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Summary—Eighty-six kidneys in 82 patients have been assessed by diuresis renography after pyeloplasty. A non-obstructed diuresis renogram was found in 64% of kidneys. Ninety per cent of patients were clinically improved by surgery and 51% of cases studied had improved urographic features. Thirty kidneys (29 patients) were assessed both before and after pyeloplasty. An improvement in the diuresis renogram was found in 89% of cases post-operatively. Standard renography demonstrated improved drainage in only 33% of kidneys. These findings are discussed in relation to the value of diuresis renography after pyeloplasty.

The clinical results of pyeloplasty for pelviureteric junction obstruction are generally very good and most patients are relieved of their symptoms or at least considerably improved (Anderson, 1963; Notley and Beaugie, 1973). The post-operative radiological features, however, are often disappointing (Johnston and Kathel, 1972; Roberts *et al.*, 1972). There is a tendency for dilatation of the pelvicaliceal system to persist despite the relief of obstruction. Even though ureteric filling with contrast media may improve on the post-operative intravenous pyelogram, there may still be a partial obstruction at the pelviureteric junction if there is persistent proximal dilatation. Alternatively, the residual pelvicaliceal dilatation after pyeloplasty may be due to hypotonicity, there being no genuine obstruction of the renal pelvis.

Diuresis renography has recently been shown to be useful in distinguishing between obstructive and non-obstructive dilatation of the renal pelvis (O'Reilly *et al.*, 1978; Lupton *et al.*, 1979). The results of this test in the assessment of pyeloplasty cases, some of which have been studied before and after surgery, have now been analysed. The aims of this study are (*a*) to determine the incidence of obstructive and non-obstructive diuresis renogram patterns after a pyeloplasty; (*b*) to compare the results of diuresis renography with clinical and radiological findings; (*c*) to compare pre-operative and post-operative diuresis renograms, where applicable. An assessment has also been made of the additional information gained by the use of diuresis renography as compared with standard renography in the evaluation of post-operative dilatation of the renal pelvis.

Patients and Methods

Diuresis renography has been used to assess 86 kidneys in 82 patients after pyeloplasty. The age range of the patients was between 2 and 69 years (mean 25.2 years) and the period since operation ranged from 2 weeks to 25 years (mean 3.3 years). The operations performed are shown in Table 1. In 53 patients (56 kidneys), the assessment was post-operative only, diuresis renography not having been carried out prior to surgery. In 29 patients (30 kidneys), however, diuresis renography was performed both before and after operation and it was therefore possible to assess changes in function and excretion resulting from surgery.

The diuresis renograms were performed using the methodology previously described (O'Reilly *et al.*, 1978; Lupton *et al.*, 1979) which may be summarised thus: standard probe renography

Table 1 Operations

Anderson-Hynes	70
Y-V plasty	8
Culp	3
Not stated	5

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

was performed with patients in a normal state of hydration. The renogram was then repeated with the patient under the influence of a diuretic stimulus (0.5 mg/kg body weight of frusemide). If on standard renography there was no elimination of the tracer from the affected kidney at about 20 min after the start of the test, it was convenient to give the diuretic at this stage and to observe the response while the tracing continued uninterrupted. On the basis of the examination of standard and diuresis renograms, or the single tracing before and after diuresis, patients with post-operative dilatation of the renal pelvis were divided into 4 groups:

Group I	Both standard and diuresis renograms were normal, excluding obstruction.
Group II	Both renograms had an obstructive pattern—the response of a severe obstruction to urine flow.
Group IIIa	The initial renogram tracing was obstructive but rapid tracer elimination occurred after diuresis—the pattern of a non-obstructed, hypotonic system.
Group IIIb	Standard renography indicated an obstructive pattern and frusemide produced only a slight improvement in elimination—the response of a partial obstruction to urine flow.

Patients have been categorised clinically as (1) symptom-free, (2) having minimal symptoms referable to the urinary tract and (3) having significant symptoms which are unchanged from or worse than pre-operatively. Intravenous urography was performed post-operatively in 55 patients (57 kidneys). In most of these cases it was possible to compare pre-operative and post-operative radiological features. Kidneys were assessed as normal, improved or unchanged, based on features such as function, cortical thickness and pelvicaliceal dilatation.

Results

The results of diuresis renography performed post-operatively in this series of 82 patients are shown in Table 2. Of the 86 kidneys assessed, a non-obstructive diuresis renogram pattern was found in 55 (64%). An obstructed diuresis renogram was present in 18 kidneys (20.9%) and there was an equivocal response to diuresis or a poorly functioning kidney in 13 instances (15.1%).

Table 2 Post-operative Excretion on Diuresis Renogram—86 Kidneys (82 Patients)

I (Normal)	5	(5.8%)	non-obstructed
IIIa (Hypotonic)	50	(58.2%)	
II and IIIb (Obstructed)	18	(20.9%)	
Equivocal	8	(9.3%)	
Poor function	5	(5.8%)	

The clinical results of pyeloplasty in this study are shown in Table 3. It must be emphasised that the group of patients who were classified as "improved" included a majority with minimal symptoms attributable to the urinary tract, often experienced on only one occasion. Seventy-four patients (78 kidneys) were symptom-free or considerably improved after surgery (90.2%). Of these kidneys associated with minimal or no symptoms, obstruction was excluded on diuresis renography in 53 of 78 (68%), whereas an obstructive pattern was present in 13 of 78 (16.7%). The remaining 12 cases (15.3%) showed an equivocal response or poor function on diuresis renography. Of the 8 kidneys (8 patients) associated with significant symptoms, unchanged from or worse than pre-operatively, an obstruction was present on diuresis renography in 5 patients (62.5%). A non-obstructive pattern was found in 2 cases (25%) and an equivocal response in one case. There was therefore a tendency for a good clinical result to be associated with a non-obstructive diuresis renogram, whereas persistent symptoms were more commonly associated with an obstructive pattern on diuresis renography.

The radiological results are shown in Table 4. In 19 of 29 kidneys with improved features radiologically, a non-obstructive diuresis renogram pattern was found (65.5%) and 6 kidneys (20.7%) had an obstructed diuresis renogram. An obstructive pattern was found on diuresis renography in only 9 of 20 kidneys (45%) with unchanged or apparently worse features on intravenous urography and a non-obstructive diuresis renogram pattern was present in 5 cases (25%). There was therefore not a consistent relationship between the diuresis renogram findings and the urographic features.

Table 3 Clinical Results of Pyeloplasty —82 Patients

Symptom free	52	(63.4%)
Improved	22	(26.8%)
Worse or unchanged	8	(9.8%)

Table 4 Radiological Results—57 Kidneys (55 Patients)

Normal	3	(5.3%)
Improved	26	(45.6%)
Unchanged or worse	20	(35.1%)
Persistent hydronephrosis— no pre-operative comparison	8	(14.0%)

Thirty kidneys (29 patients) were assessed by diuresis renography both before and after pyeloplasty. The post-operative diuresis renogram was performed at periods ranging from 2 weeks to 2½ years (mean 8 months) after operation. The function assessed renographically was improved by surgery in 10 kidneys (33.3%). There was no change in the function of 16 kidneys (53.3%) and in 4 cases (13.4%) the function had deteriorated. The results of the excretion determined by diuresis renography are shown in Table 5. Of the 27 kidneys with an obstructive pattern, an equivocal response or poor function pre-operatively, 20 (74.1%) were improved by surgery to either a hypotonic response or to normal. Figures 1 and 2 show a typical case in which a pre-operative obstructed diuresis renogram is converted to a non-obstructive pattern by pyeloplasty. A further 4 kidneys (14.8%) showed an improvement in excretion but an obstructive pattern persisted in 2 of these and an equivocal response was found in the other 2 cases. No change was found in one patient and a deterioration in the diuresis excretion response in a further 2 cases. There was therefore an improvement in excretion after surgery as assessed by diuresis renography in 24 kidneys (88.9%) and no change or a deterioration in 3 cases (11.1%).

Discussion

There has been considerable debate concerning the value of conventional renography in the assessment of the results of pyeloplasty. Some authors have found the renogram to be useful in this situation (Santiago, 1969; Hizazumi *et al.*, 1972; Karlberg, 1976), while others have considered this test to be of little value (Roberts *et al.*, 1972; Whitaker, 1973). Davies *et al.* (1969) found an improvement in the shape of the renogram after surgery in 70% of cases. It was observed that the lack of improvement in drainage in half of these patients may have been due to a persistently capacious renal pelvis even though obstruction had been relieved. Tveter *et al.* (1975) found a good correlation between the results of urography and renography in the assessment of pyeloplasty cases. In another series, Otnes *et al.* (1975) demonstrated marked differences between radiological and renographic findings after pyeloplasty.

Table 5 Diuresis Excretion Response—Before and After Pyeloplasty—30 Kidneys (29 Patients)

Before		*After*		
Obstructed	21	Non-obstructed	20	(74.1%)
Equivocal	2	Improved	4	(14.8%)
Poor function	4	Unchanged	1	(3.7%)
		Worse	2	(7.4%)
Non-obstructed	3	Non-obstructed	3	

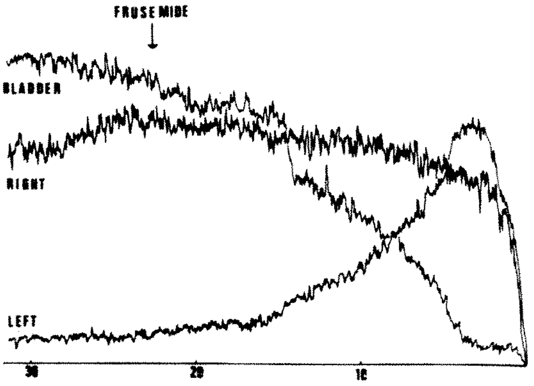

Fig. 1 Pre-operative diuresis renogram in a patient with a right idiopathic hydronephrosis. Normal bladder and left kidney tracings. Right kidney shows an obstructive renogram pattern both with and without a diuretic stimulus.

Two further reports have emphasised the shortcomings of conventional renography in the diagnosis of obstruction after a pyeloplasty but have proposed methods of manipulating renogram data to gain more information. Johnston and

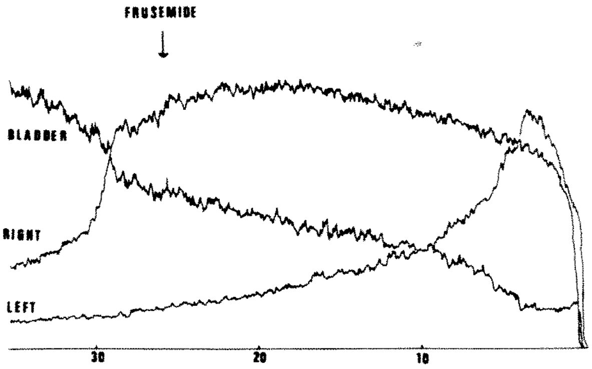

Fig. 2 Post-operative diuresis renogram in the same patient. Frusemide produces a significant improvement in excretion from the right kidney, indicating a hypotonic system.

Kathel (1972) found an improvement in drainage from 29 of 32 kidneys after pyeloplasty when using quantitative assessments with analogue computer simulation. These results were better than those of conventional renography (9 kidneys improved) and urography (50% improved). In another series using deconvolution analysis of gamma camera renograms, Whitfield *et al.* (1978) found an improvement after pyeloplasty in 8 of 9 kidneys which were renographically obstructed pre-operatively.

In the present study, while an assessment of symptoms indicated that over 90% of patients were significantly improved by the operation, the diuresis renogram showed an improvement in excretion in only 64% of kidneys. The results of diuresis renography were, however, better than the radiological results, only 51% of kidneys showing a definite improvement on intravenous urography. It is likely that the rather high incidence of kidneys with obstructed diuresis renograms in this overall series (20.9%) was in part due to the fact that the patients examined only post-operatively were not necessarily representative of the pyeloplasty population as a whole. Some of these patients were examined by diuresis renography because of disappointing clinical or radiological results several years after pyeloplasty, when many of their contemporary pyeloplasty patients had already been discharged from follow-up and not referred for post-operative renography. This overall series was therefore not consecutive for pyeloplasty cases but was virtually consecutive for those patients who had been referred for post-pyeloplasty diuresis renography between late 1976 and early 1979.

Of the 30 kidneys assessed both before and after pyeloplasty, 27 had an obstructive pattern, an equivocal response or poor function on diuresis renography pre-operatively. In 88.9% of these cases, the post-operative diuresis renogram showed improvement in the function and/or excretion of the affected kidney. The early post-operative assessment of these cases had therefore indicated very good results from pyeloplasty and it will be interesting to see if these are maintained over the course of several years. Standard renography demonstrated an improvement in drainage post-operatively in only 33% of kidneys and therefore diuresis renography contributed considerably more information on the results of surgery.

In the series overall (86 kidneys), there was an equivocal diuresis renogram or poor function post-operatively in 13 instances, so that a definite answer could not be given on the excretion from the renal pelvis. In only 5 kidneys was the standard renogram normal. In 68 cases (79.1%), therefore, the response of the third phase of the renogram to the diuretic was informative and indeed necessary to determine the presence or absence of obstruction on probe renography. It is concluded that the diuresis renogram is of significant value in assessing the surgical results of pyeloplasty.

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The Early and Aggressive Repair of Iatrogenic Ureteric Injuries

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Summary—Sixty-two iatrogenic injuries of the ureter in 52 patients have been studied over a 15-year period. A plea is made for early recognition of post-operative urinary fistulae and early operative repair. The results of 41 cases treated by the Boari-Ockerblad method are reported without post-operative obstruction or failure.

Iatrogenic injuries of the ureter are fortunately uncommon, for their surgical repair can be exceedingly difficult, especially when there has been loss of ureteric length, infection, irradiation or previous unsuccessful attempts at repair. Failure of repair is paid for in terms of fistulae, obstruction, infection and sometimes even septicaemia. Hence it is widely recognised that the first attempt at repair should be the definitive one if possible. This raises 2 questions: (1) when should the repair be attempted? and (2) how should it be performed? To allow inflammation and oedema to resolve, it is often recommended that one should delay the repair for 6 to 8 weeks after the original injury to the ureter: this we dispute, having always attempted to repair the injury as soon as the patient's general condition permits (Blandy and Anderson, 1977). For the repair one may choose between the Boari-Ockerblad flap (Boari, 1894; Ockerblad, 1947), reimplantation with the psoas hitch (Ehrlich *et al.*, 1978) or transureteroureteric anastomosis (Smith and Smith, 1975). Having used the Boari flap over the last 15 years in most of our cases, we thought it right to see how its results compared with these alternatives.

Patients

Sixty-two ureteric injuries in 52 patients were referred over the 15-year period 1964 to 1979 with follow-up from 5 months to 15 years.

There were 35 women and 17 men, a ratio of 2:1, with an age range of 19 to 71 (mean 47 years). The majority of the injuries occurred below the pelvic brim (Fig. 1): there were 2 unusually high injuries: one followed a misguided but successful Dormia extraction of a high ureteric stone which was followed by tearing across and intussusception of the ureter: the other followed an attempted pyeloplasty in another hospital.

The causes of the ureteric injury are shown in the Table. Thirty-three of the 62 ureters were injured in the course of hysterectomy or other gynaecological operations, in 8 cases after previous radiotherapy, and in 2 during difficult emergency Caesarean-hysterectomy for ruptured uterus. The ureter was at risk during operations

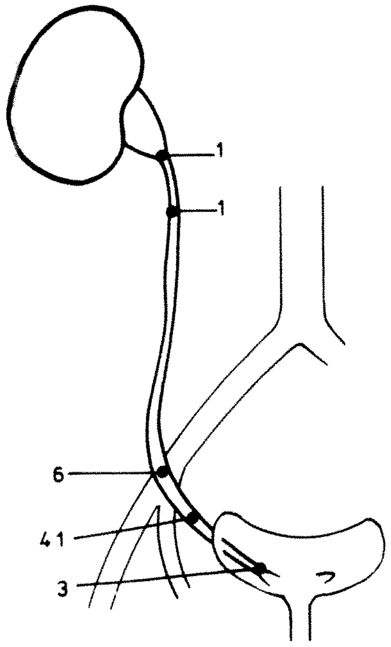

Fig. 1 Sites of ureteric injuries in 52 patients.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table Ureteric Trauma—Aetiology in 52 Patients

Cause	*Patients*	*Ureters*
Hysterectomy, etc.	26	33
Ureteric stone	8	8
Other urological operations	6	6
Bowel resection	8	10
Aortic and iliac artery	2	3
Surgery for fractured pelvis	2	2
Total	52	62

for bowel resection and removal of ureteric stones, and the wide variety of these injuries should serve as a warning that the ureter is always at risk during any retroperitoneal or pelvic dissection.

Clinical Features

In only one of the cases in this series was the injury to the ureter noticed at the time of the original operation (a Wertheim's hysterectomy after radiotherapy): an unsuccessful attempt at repair was made to the left ureter, a coincident injury to the right escaped notice.

Four patients with bilateral injury presented with post-operative anuria suggesting acute tubular necrosis.

Forty-four per cent presented with a leak of urine: in some this occurred early, but seems to have gone unnoticed. In others there was a distinct interval between the operation and the onset of the leakage of urine, usually about 10 days, and often after the patient had left hospital. In retrospect the notes often record prolonged ileus and slow recovery.

Obstruction seems to have been a constant feature after ureteric injury and led to loin pain in 17 patients and infection in 7. Septicaemia was present in 2 of the patients when bilaterally obstructed ureters led to anuria.

In 2 patients investigation of hypertension up to 8 months after the injury led to the detection of the lesion: 2 others were detected in urological patients in a routine follow-up urogram.

Investigations

Urography Hydronephrosis was present in 48 kidneys (92% of the patients). Fistulae were shown in the urogram in 11 cases.

In the 4 anuric patients contrast was only detectable, if at all, in delayed films.

In 6 patients hyperkalaemia and uraemia required dialysis before diagnosis or repair could be attempted.

Cystoscopy and Ureterography Immediately before attempting any repair, cystoscopy (to exclude vesicovaginal fistula) and bilateral ureterography (to check on the other side) now form part of our routine practice.

Method of Surgical Repair

In 41 patients the technique was the Boari-Ockerblad method (Blandy, 1978) incorporating minor modifications to ensure that the flap was of adequate length to avoid tension by carrying it across the bladder, and that a long submucosal tunnel was made to prevent reflux. The ureter was splinted for 10 to 14 days with a 6 to 8 FG Gibbon catheter attached by its flaps to the skin.

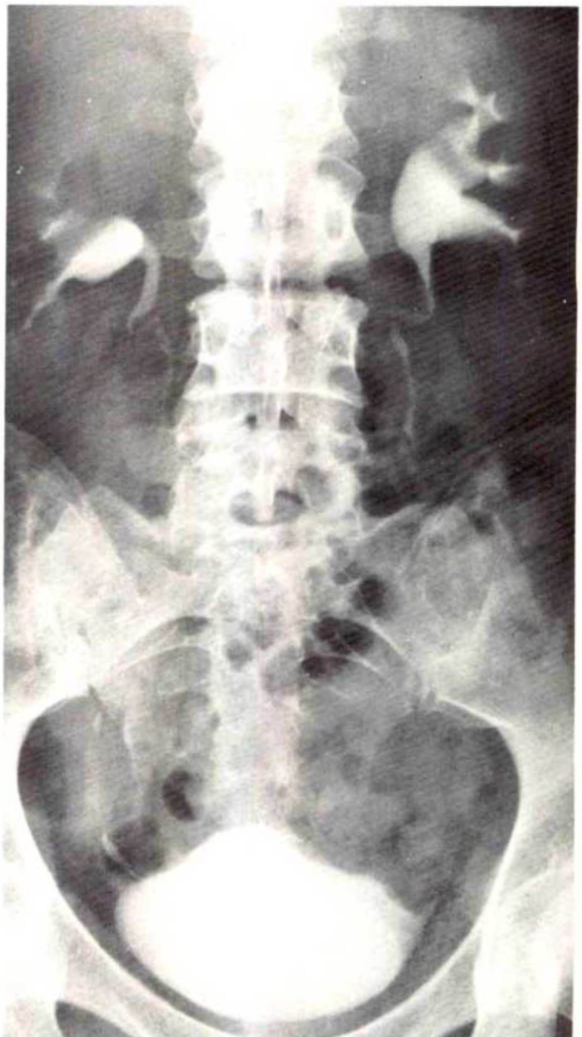

Fig. 2 Intravenous urogram after Boari-Ockerblad flap.

In most cases the tip of the bladder flap was sutured to the psoas minor tendon to keep ureter and tube aligned. When suturing the Boari tube the opposite ureter was protected by a catheter. The wound and bladder were drained suprapubically.

In 5 cases the ureter was reimplanted directly to the bladder: 4 of these failed. Two underwent nephrectomy, but 2 were later salvaged with a Boari flap.

The psoas hitch reimplant method was used successfully in 3 cases.

Nephrectomy was performed in 4 patients who had poorly functioning kidneys. One very obese woman, who continued to bleed after Caesarean section, an emergency hysterectomy and re-exploration and ligature of an internal iliac artery, was known to have had one ureter ligated. After a prolonged convalescence a functionless kidney was detected by urogram and scan, and left alone.

Results

Follow-up urograms were performed in all but 2 patients, who were allergic to the contrast medium. In 15 there was residual hydronephrosis: in the remainder the kidneys appeared normal. Cystograms were performed only when the appearance of the pyelogram or continuing symptoms seemed to justify the investigation: reflux was detected in 2 patients, but there has been no deterioration in these kidneys during the period of the review.

Fifty-two ureters were repaired with Boari-Ockerblad flaps; in 2 cases the flaps were taken up to the level of the pelviureteric junction.

The post-operative appearances of the bladder all showed good emptying, the flap often being undetectable (Fig. 2). Sometimes the flap was seen as a diverticulum and, when bilateral, sometimes presented a bizarre appearance (Fig. 3). After a few months the bladder capacity returned to normal. Only one patient, with radiotherapy and bilateral Boari reimplantation of the ureter, had any disturbance of continence (occasional enuresis).

Discussion

Whenever possible early surgical exploration was undertaken, and this has not given rise to any extra difficulty: on the contrary, it is our impression that the longer the repair is delayed, the more difficult becomes the dissection because of the denseness of the fibrous tissue. Our policy of early and aggressive repair has not been altered by this review of our results. In practice, early recognition and prompt repair of the injury make for a quick recovery and lessen the distress of the patient and her family. Whenever possible, we prefer to effect the repair during the patient's first admission to hospital. However, this calls for early recognition of the injury and, in particular, more widespread awareness that "leakage" during the post-operative period after hysterectomy calls for prompt measurement of the urea in the fluid collected.

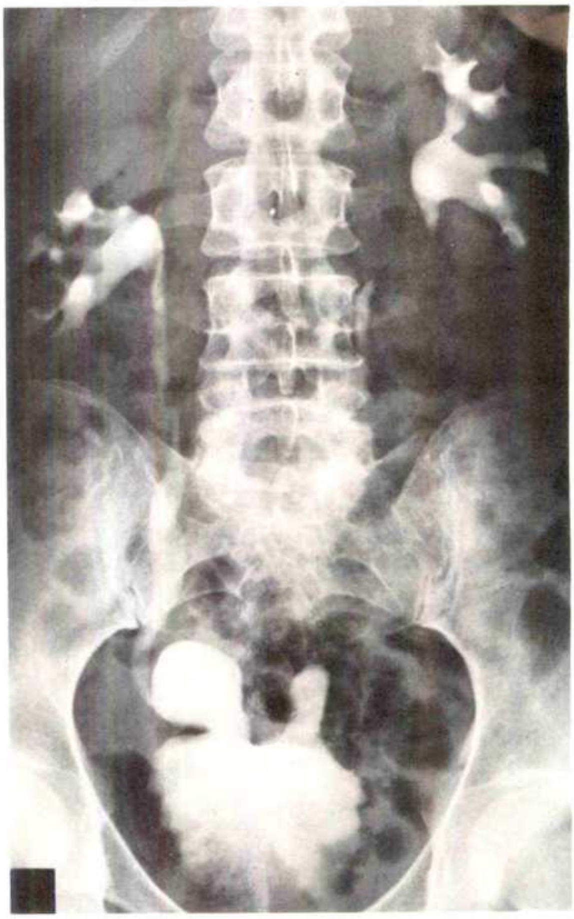

Fig. 3 Bilateral Boari-Ockerblad flaps.

Tests using methylene blue in bladder and ureter, or the study of tampons in tandem in the vagina, are of little value. Careful cystoscopy and bilateral ureterography under image intensifier control are essential, for a normal urogram does not rule out ureteric injury.

This experience with the Boari flap shows that the operation is not difficult to perform and gives good results even when a long gap has to be bridged or there has been previous operative intervention or radiotherapy. For this reason we have been reluctant to risk injury to the other ureter by transureteroureterostomy. Good results have, of course, been obtained by some (Smith and Smith, 1975) but not always by others (Ehrlich and Skinner, 1975; Sandoz *et al.*, 1977). The mobilisation of the other side of the bladder which is needed to make the psoas hitch suggests that this is hardly less of an operative procedure (and in one case in this series was the cause of the ureteric injury) than the formation of a Boari flap. A psoas hitch may give excellent results (Ehrlich *et al.*, 1978), but for the time being we see no reason to abandon the Boari flap.

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The Long-term Results of Ileal Conduit Urinary Diversion in Children

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Summary—Sixty-seven children undergoing urinary diversion by ileal conduit tolerated this procedure well. The initial results were most satisfying, but late complications occurred in 55 children (82%), and this is a cause for concern. Even when the surgical complications were avoided, it seemed important to consider carefully the psychological problems that these children with ileal loop diversion could develop as they advanced into adult life.

Urinary diversion has been practised for well over a century but it has only recently become popular with the introduction of the ileal loop urinary conduit (Bricker, 1950).

Ileal loop conduit has been recommended in the management of a wide variety of disorders of the urinary tract in children. A sufficient period of time has now elapsed for the long-term results to be assessed and it is becoming apparent that few children fail to develop late complications following ileal loop conduit diversion.

Sixty-seven children have had urinary diversion by means of ileal conduit over the last 20 years (mean 10.2 years) in the Department of Urology, United Bristol Hospitals. Fifty-eight (87%) were female and the underlying disorders of the urinary tract and the symptoms leading to urinary diversion are shown in Tables 1 and 2.

We describe here the late complications that we have encountered (Table 3). Late complications occurred in 55 children (82%).

Patients and Methods

Stomal Obstruction

Stomal problems were by far the most common late complication of ileal conduit diversion (Table 3) and frequently necessitated stoma revision. The cause of stomal obstruction was often impairment of the blood supply of the stoma, usually at the site where the conduit passes through the deep fascial layers of the anterior abdominal wall. This impairment led to progressive fibrosis of the wall of the conduit, causing it to shorten and narrow. Eventually, the stoma became flush with the anterior abdominal wall, making collection of urine increasingly difficult and leading to excoriation around the stoma with the development of hyperkeratosis and encrustation of the stoma, which compounded the degree of obstruction. The late stomal problems occurring in this series were varied (Table 4).

The other major cause of stoma obstruction was ill-fitting stomal appliances. Some patients who developed stoma obstruction did so as a result of ill-fitting appliances over a prolonged period of time. This cause has now been considerably reduced by the development of stoma care clinics with trained stomatherapists. Some of the stomal problems have been managed successfully by conservative means but further surgery has often been necessary (Table 5).

Upper Tract Dilatation

The primary reason for undertaking this radical form of surgery in many cases was to protect the

Table 1 Indications for Ileal Loop Urinary Diversion

Neuropathic bladder	
Spina bifida*	58
Transverse myelitis	2
Spinal tumour	2
Disseminated sclerosis	1
Poliomyelitis	1
Ectopia vesicae*	3
Rhabdomyosarcoma of prostate	1
Total	67

* One child had both spina bifida and ectopia vesicae.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 2 Symptoms and Investigative Findings Leading to Ileal Loop Urinary Diversion

Incontinence	37
Progressive upper tract dilatation	28
Recurrent urinary tract infection	20
Ectopia vesicae	3
Rhabdomyosarcoma	1

upper urinary tract from damage. In the long term, despite surgery, almost a third of the children (28%) developed progressive upper tract dilatation which presumably developed as a result of either distal obstruction or severe reflux, or both.

Elongation of the Conduit

Elongation of the conduit has occurred in 16 children (24%) and was due either to growth in length of the conduit or to distal obstruction.

As a result of elongation the ileal loop became a reservoir rather than a conduit. This led to stagnation of the urine with chronic infection and deterioration in the upper urinary tracts. Ten children needed shortening of the loop, and 2 children a new conduit, because of persisting symptoms despite adequate conservative therapy.

Pyocystis

In our series 16 children (24%) developed infections in the isolated bladder, and these were all female.

In most cases urethral dilatation and bladder washout with an appropriate antiseptic or antibiotic solution were sufficient. In a few children urethral dilatation and bladder washout were unsuccessful; a vesicovaginal fistula was created in one girl and cystectomy was done on 2 children.

Table 3 The Late Complications of Ileal Loop Urinary Diversion

Stomal problems	33
Progressive upper tract dilatation	19
Redundant loop	16
Pyocystis	16
Recurrent severe infections	13
Psychological problems	18
Ureteroileal obstruction	3
Small bowel obstruction	3
Renal stones	8
Ureteric stones	2
Conduit stones	2
Parastomal hernia	1
Volvulus of conduit	1
Spontaneous perforation of conduit	1

Table 4 Stomal Problems in 33 Children (49%)

Stomal obstruction	25
Flush stoma	11
Ulceration of and bleeding from stoma	7
Stomal encrustation	4
Severe peristomal skin reaction	3
Prolapsed stoma	2

Table 5 Management of Stomal Problems

Conservative	9
Surgical	24
Refashioning of stoma	20*
Resiting of stoma	4

* Five patients required a second refashioning and 2 a third.

Severe Recurrent Infections

Thirteen children (20%) presented with severe recurrent urinary tract infections which were found to be due to either stomal obstruction or ureteroileal obstruction.

Psychological Problems

A large group of patients (27%) suffered distinct psychological complications as a result of urinary diversion. Many of these complications became apparent at puberty. The psychological problems could be split into 3 well defined groups—educational, social and sexual.

The children with ileal loop diversion needed to attend special schools for the disabled. Educational problems were created by the lack of contact with normal children and teachers. Many children, especially as they got older, tended to restrict their social life because of the diversion. Finally, there were an increasing number of sexual problems as these children grew into young adults. A detailed assessment of these psychological problems is being made at present with our psychiatric colleagues. The following case demonstrates an example of the problems that can be encountered.

Case Report

A 13-year-old girl with poliomyelitis was left with a neuropathic bladder which somewhat unusually was the only residual lesion of the disease. Urinary tract diversion was finally undertaken to relieve both severe urge incontinence and recurrent urinary tract infections leading to pyelonephritis. Following the diversion, the patient married and had 2 children. However, she has had an extremely stormy married life. Initially, her husband deserted her for a variety of other women, blaming the stoma for his infidelity. Paradoxically, when the marriage appeared to be stabilising, the girl has left him on 2 occasions for other men. Psychiatric assessment indicated that it was the need to demonstrate her femininity, despite the existence of her ileal stoma, that precipitated her infidelity.

Ureteroileal Obstruction

Ureteroileal obstruction could occur at any time during the follow-up period. It was usually discovered on excretion urography with progressive upper tract dilatation. The site of the obstruction was defined by means of a loopogram, the absence of ureteric reflux from the ileal conduit being practically diagnostic of ureteroileal obstruction. Three patients with severe ureteroileal obstruction in this series all required exploration and reconstruction of the ureteroileal anastomosis.

Intestinal Obstruction

Intestinal obstruction has occurred both very early in the post-operative period and also as a late complication as much as 10 to 15 years after ileal conduit diversion. In 2 of the 3 children the obstruction has been managed successfully by conservative means, whilst in the third a laparotomy was performed.

Stone Formation

Eight children developed renal stones. In 2 children a ureteric calculus presented with classical ureteric colic, and in both cases the stone had to be removed. Finally, 2 children developed large conduit stones both of which had to be removed surgically.

Miscellaneous

One child presented 8 years after diversion with an acute abdomen and at laparotomy was found to have volvulus of the conduit. One child developed a parastomal hernia of some size and this was repaired surgically. The final late complication encountered was that of urine peritonitis due to perforation of the conduit some 14 years after diversion. The perforation was caused by the conduit being strangulated by an adhesion.

Discussion

The high incidence of late complications of ileal loop diversion in children in this series (82%) is comparable with those reported by Schwarz and Jeffs (1975) and Shapiro *et al.* (1975).

Progressive upper tract dilatation following urinary diversion has been reported in 10 to 42% of cases (Susset *et al.*, 1966; Smith, 1972); in this series it was 28%. In view of these significant rates of urographic deterioration, perhaps the indications for urinary diversion in children with pre-operative normal urograms should be critically reviewed, since it would seem impossible to predict whether these children would have progressed to such deterioration with further conservative management without diversion.

Severe recurrent urinary tract infections would seem to be an index of failure of conservative treatment and a poor prognostic sign after diversion. Three potentially preventable and surgically correctable late complications of ileal conduit diversion, namely stomal stenosis, excessive conduit length and ureteroileal obstruction, have been shown to affect the long-term objective results for renal structure and function (Schwarz and Jeffs, 1975). These and other unpredictable late complications of diversion, such as stone formation, emphasise the need for life-long thorough follow-up.

Psychological problems represent a most significant late complication of urinary diversion in children. It is vital to get the children back into the everyday life of the community. The psychological problems developing after ileal loop urinary diversion may well have been grossly underestimated in the past. Shapiro *et al.* (1975) state that every child with ileal loop urinary diversion for reasons other than a neuropathic bladder must be considered a potential candidate for undiversion since the late results of ileal loop diversion were so unsatisfactory.

The reported incidence of late complications in a similar group of children who have had colonic conduit urinary diversion and ureterosigmoidostomy (Altwein *et al.*, 1977) was much lower. Following colonic conduit diversion only 14.5% of children developed late complications, whilst only 20% of children developed late complications following ureterosigmoidostomy.

It is now our policy to adopt a more conservative approach to those conditions for which urinary diversion has been advocated in the past. Intermittent clean catheterisation is being tried and has been shown (Plunkett and Braren, 1979) to be an effective alternative to supravesical diversion in preserving upper urinary tract function in children with neuropathic bladder. When urinary diversion is performed colonic conduit diversion is now preferred.

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A Long-term Follow-up of the Colonic Conduit Operation in Children

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Summary—The results of colonic conduit urinary diversion have been reviewed in 41 children with an average follow-up of 13.2 years. There was a high incidence of stomal stenosis (61.5%), ureterocolic stenosis (22%), ureteric reflux (58%) and upper tract deterioration (48.4%). Comparison with results of ileal conduit diversion in children show no advantage in the use of colon.

For many years the accepted procedure for urinary diversion was ureterosigmoidostomy. This operation fell into disrepute, however, because of problems with ureteric reflux, upper renal tract deterioration and electrolyte imbalance (Goodwin and Scardino, 1977).

In the early 1950s the ileal conduit became the most popular method of diversion (Bricker, 1950). Early results of this operation were promising, but longer term follow-up studies revealed a high incidence of complications, in particular stomal stenosis and renal deterioration (Richie, 1974; Schwartz and Jeffs, 1975; Shapiro *et al.*, 1975).

In the early 1960s the colonic conduit was popularised as a method of diversion by Mogg (1965) and early reports of its use have been encouraging (Altwein *et al.*, 1977; Althausen *et al.*, 1978). Emphasis was placed on the low incidence of stomal stenosis and the ease with which an antireflux mechanism could be formed in the thicker wall of the colon.

This paper reviews the longer term results in 41 children who have had colonic conduit urinary diversion.

Patients and Methods

The records of 48 patients who had colonic conduits constructed between 1957 and 1967 were reviewed (Table 1). There were 24 males and 24 females ranging in age at the time of operation from 1 to 12 years (average 5.4 years). Seven patients were untraceable or refused attendance for review. There were 15 deaths in the series. Thus 26 patients were fully assessed. They had a follow-up period of between 9 and 20 years (average 13.2 years).

Table 1 Indications for Diversion

Neuropathic bladder secondary to spina bifida	32
Ectopia vesicae	7
Congenital bladder neck obstruction	1
Unknown	8
Total	48

Each operation was performed using a standard technique (Mogg, 1975). This involved mucosa-to-mucosa ureterocolic anastomosis, formation of an intraluminal nipple and construction of a short submucosal tunnel.

Patient review included the anatomical appearance of the stoma and the functional effectiveness of the urostomy appliance. Blood urea and electrolytes were measured. A current intravenous urogram and conduitogram were available for all patients. A catheter specimen of urine was collected from the depths of the conduit after cleansing the stoma.

As 2 patients had an agenetic kidney, there were 50 separate renal units available for assessment.

Results

Mortality

Five patients died in the peri-operative period (Table 2). There were 10 late deaths (24.4%) of which 5 were due to renal failure. Of this latter group 3 patients had severely compromised upper tracts at the time of surgery.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 2 Cause of Death

Peri-operative	5
Renal failure	5
Peritonitis	1
Bowel obstruction	1
Septicaemia	1
Unknown	2
Total	15

Stomal Complications

At review 3 patients had stomal stenosis, 3 patients had peristomal dermatitis and there were 5 cases of minor prolapse.

Twelve patients had problems with the fitting or design of their urostomy bag and needed a different type of appliance. This was due to leakage at the skin/appliance interface occurring more frequently than every third day. Some of these functional difficulties were secondary to an anatomical problem.

There were only 10 out of the 26 children whose stoma and appliance function could be considered normal.

Overall during the follow-up period, stomal stenosis requiring corrective procedures occurred in 61.5% of patients, some patients requiring multiple procedures (Table 3). Surgical revision was performed on 13 patients and 3 were treated with dilatation alone. The occurrence of stomal stenosis bore no relation to the age of the patient at the time of the original operation. The incidence of stenosis increased in direct proportion to the length of follow-up.

Stomal prolapse required surgery in 4 patients.

Ureterocolic Stenosis

Eleven patients needed correction of stenosis at the ureterocolic anastomosis, 7 during the follow-up period, and a further 4 patients had stenosis detected at review. This is a total incidence of 22%.

Table 3 Incidence of Stomal Stenosis (N = 26)

Method of treatment	*Number of patients*
1 Revision	7
2 Revisions	3
3 Revisions	1
4 Revisions	1
5 Revisions	1
Dilatations	3
Total	16

In all of these patients there was a deterioration in the radiographic appearances of the upper tracts, even in those which had been surgically corrected.

Calculi

Staghorn calculi developed in 6 patients, and 2 of these were affected bilaterally. In 4 of the affected renal units there was obstruction at the stoma or the ureteric anastomosis and in the other 4 there was ureteric reflux.

One ureteric stone occurred above a ureterocolic stenosis. Two patients had calculi removed from their conduit.

Electrolyte Disturbance

Hyperchloraemic acidosis was present in 3 patients. Two of these had a significant blood urea elevation. Urinary stasis present in 2 of these patients was related to stomal stenosis in one and a capacious conduit in the other.

Infection

A pure culture of greater than 10^5 organisms per ml was grown from 11 conduits. A mixed culture was obtained in 3 cases. The organisms were *Proteus, Pseudomonas, Esch. coli* or *Streptococcus*. Three patients had associated loin pain

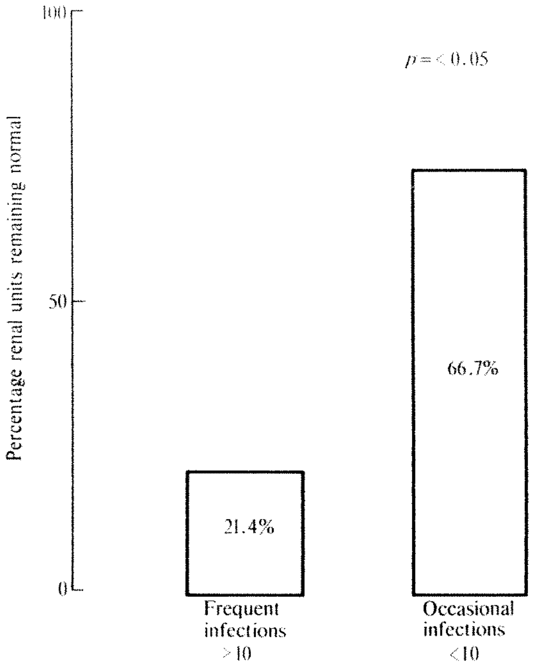

Fig. 1

Table 4 Change in Status of 46 Upper Renal Tracts between the Pre-operative Period and Review

Pre-op.		*At review*	
Normal	31	Normal	16
		Deteriorated	15
Abnormal	15	Improved	2
		Deteriorated	13

Table 5 Incidence of Late Complications

Stomal stenosis	16/26 (61.5%)
Stomal prolapse	4/26 (15.4%)
Electrolyte disturbance	3/26 (11.5%)
Renal calculi	8/50 (16%)
Ureterocolic stenosis	11/50 (22%)
Reflux	29/50 (58%)
Death (late)	10/41 (24.4%)

and several complained of offensive-smelling urine.

Analysing the frequency of recorded urinary infections during the follow-up period it was found that patients could be divided into 2 groups—those with frequent (>10) and those with occasional (<10) urinary infections (Fig. 1). Of those renal units exposed to frequent infections only 3 out of 14 (21.4%) remained normal, while in those with occasional infections 10 out of 15 (66.7%) remained normal ($P = <0.05$).

Status of Upper Renal Tract

At the time of the original operation 31 renal units were normal and 15 were abnormal (Table 4). There was no record in 4 units. Fifteen (48.4%) of the normal units deteriorated during the follow-up period.

Only 2 units improved, and this was associated with the creation of a successful antireflux mechanism in dilated ureters. In the 9 other dilated ureters, reflux was not prevented and there was progressive deterioration in radiographic appearances.

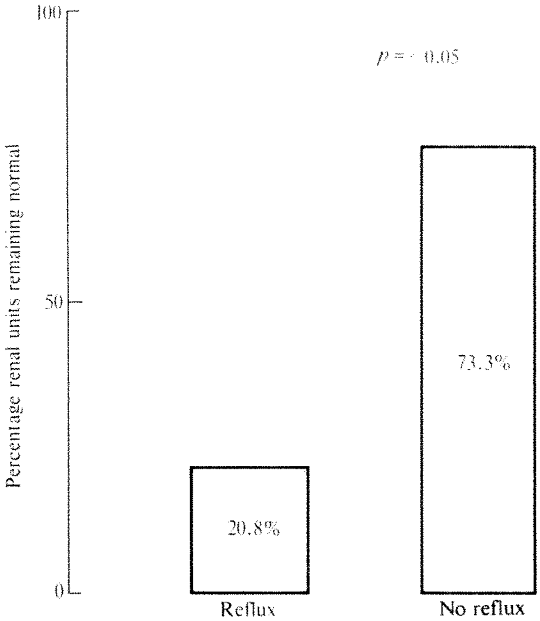

Fig. 2

Ureteric Reflux

A refluxing ureter was defined as one with any degree of reflux noted at any time during follow-up. Using these criteria, reflux was recorded in 29 out of 50 renal units (58%). In 8 units reflux was intermittent on serial conduitograms.

Excluding units subjected to obstruction, it was found that of the refluxing renal units only 5 out of 24 (20.8%) remained normal, while of the non-refluxing units 11 out of 15 (73.3%) remained normal ($P = <0.005$) (Fig. 2).

Discussion

The aim of urinary diversion should be to protect the upper renal tracts from significant damage over an average life span and enable the patient to live a normal existence. This aim is especially important in children born with neuropathic bladders, many of whom are otherwise unaffected.

In view of the encouraging short-term results with colonic conduit diversion, it is surprising to find such a dramatic increase in the incidence of complications amongst patients in this series (Table 5). Indeed, of the 26 surviving children there were only 7 who could be considered to have had a good long-term result from the operation, with normal upper tracts, no reflux and satisfactory stomal function.

Uncorrected stomal stenosis leads eventually to dilatation of the conduit, stasis and urinary infection. In the presence of reflux, upper tract damage is then hastened. Hyperchloraemic acidosis can occur secondarily to these changes and there is also a predisposition to stone formation in the conduit.

Ureterocolic stenosis leads to particularly rapid upper tract deterioration. It often occurs insidiously and emphasises the need for regular review of the upper tract status.

Table 6 Factors which Contribute to Upper Tract Deterioration

1. Upper tract damage present at the time of surgery
2. Ureterocolic reflux
3. Ureterocolic stenosis
4. Stomal stenosis
5. Recurrent urine infection

The high incidence of ureteric reflux is particularly disappointing since the main reason for using colon as a conduit was to achieve formation of an antireflux valve.

The factors involved in the long-term deterioration of the upper tract are clearly demonstrated (Table 6). Thus diversion should ideally be performed before significant upper tract change occurs. The answer to both ureterocolic stenosis and reflux probably lies in the anastamotic technique, and it has been suggested (Goodwin and Scardino, 1977; Althausen *et al.*, 1978) that a longer submucosal tunnel may solve this problem. There are as yet, however, no long-term studies available on the results of such a modification.

The occurrence of intermittent reflux is of interest and may represent functional changes in the antireflux mechanism. Variation in conduitogram technique may, however, be responsible and therefore a standard method should be used throughout the follow-up period.

Comparison of these results with similar long-term reviews of ileal conduits (Schwartz and Jeffs, 1975; Shapiro *et al.*, 1975) reveals an incidence of stomal stenosis considerably less than those recorded here. The rates of upper tract deterioration and ureteroileal stenosis were similar. Our results indicate that decisions regarding the use of colon instead of ileum cannot be made on the grounds of a lower complication rate for colon.

Regular follow-up is a most important part of the treatment of these patients, for although it may not be possible to prevent complications, their deleterious effect on the upper tract can be reduced to a minimum by early corrective surgery. Thus an intravenous urogram and conduitogram should be obtained every 12 months, looking in particular for ureterocolic stenosis. A high index of suspicion should be maintained in the presence of reflux which has suddenly stopped. The stoma should be reviewed periodically and urinary infection effectively treated.

Stoma therapy plays an important part in the follow-up, not only to correct functional stomal problems, but to keep the patient informed about the latest urostomy equipment.

It was concluded that the early encouraging results with colonic conduits in children have not been substantiated in this series. Long-term protection of the upper tracts can be achieved if stomal stenosis, ureteric stenosis and reflux can be prevented. Further trials with alternative methods of ureterocolic anastomosis are required in order to develop a satisfactory antireflux mechanism. Regular follow-up is essential if upper tract deterioration is to be kept to a minimum.

Acknowledgement

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Tumour of the Colon as a Late Complication of Ureterosigmoidostomy for Exstrophy of the Bladder

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Summary—Two cases of cancer of the colon have occurred recently in our series of 38 patients with exstrophy of the bladder treated by ureterosigmoidostomy. Twenty-six and 14 years elapsed between the original operation and the diagnosis of malignancy. Since 1929 the literature contains reports of 55 patients who have developed bowel neoplasms as a late complication of this form of diversion. The operation was performed for exstrophy in 35 of these, in whom the resulting tumour at the anastomotic site was malignant in 28 and benign in 7 patients. The shortest interval between ureterosigmoidostomy and recognition of the growth was 10 years with a mean latent period of 25 years. The aetiology remains uncertain but it is clear that long-term survivors after ureterosigmoidostomy should have diagnostic large bowel studies included in the follow-up.

Despite its ups and downs over the years ureterosigmoidostomy still remains a useful form of urinary diversion for certain patients. Improvements in operative techniques and a better understanding of the physiological mechanisms involved when urine is shunted into the colon have either lessened the complications of obstruction, reflux infection and hyperchloraemic acidosis or made them more amenable to treatment. Amongst the indications for this method are patients with exstrophy of the bladder, in which group many long-term healthy survivors are now found. Indeed for years we have chosen simultaneous bilateral ureterosigmoidostomy at an early age as our preferred approach to the patient with exstrophy. The results achieved in our series parallel the experiences of others (Bennett, 1973; Wear and Barquin, 1973; Spence *et al.*, 1975).

Unfortunately, however, another complication is being reported with increasing frequency as the longevity of those undergoing the procedure has lengthened. This consists of malignancy of the colon developing after an interval of many years. We report 2 such occurrences from our series of 38 patients.

Case Reports

Case 1. In December 1960 at 3 months of age this male infant underwent bilateral ureterosigmoidostomy by the combined tunnel and mucosa-to-mucosa technique for exstrophy of the bladder (H.M.S.). He subsequently developed bilateral hydronephrosis necessitating a ureteroileal conduit 9 months after the initial implantation of the ureters into the colon (W.W.H.). The stumps of the ureters where they joined the sigmoid were left intact at this secondary diversion.

Thereafter the patient did well for 14 years until at age 15 he presented with rectal bleeding. Sigmoidoscopic examination revealed 2 polypoid lesions of the rectosigmoid which on biopsy were reported to be benign. Barium enema confirmed that these were the only lesions present in the bowel. The upper urinary tract and ileal conduit were functioning satisfactorily. Despite the initial pathological report, the findings at exploratory laparotomy indicated that the lesions were malignant, and so a low anterior resection of the rectosigmoid was carried out with extirpation of the node-bearing area (G.P.F.). Two polypoid masses were found, one an adenomatous polyp and the other an adenocarcinoma on histological examination. Both tumours were located exactly at and surrounding the site of the ureteric stumps which were identifiable grossly and microscopically. One mesenteric lymph node contained carcinoma. The patient is alive and well 3½ years post-operatively.

Case 2. This 27-year-old girl was seen in 1978 complaining of urinary tract infection. At age one year, 26 years previously, she had a bilateral ureterosigmoidostomy by the Cordonnier technique by one of us (H.M.S.) followed by cystectomy and reconstruction of the genitalia. She had been followed systematically and had been seen last only 2 years prior to the present admission, at which time the right kidney was entirely

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normal on intravenous pyelography. The left showed some pyelonephritic changes attributed to reflux as shown by a contrast enema.

The patient was found to have marked hyperchloraemic acidosis with an elevated blood urea. An intravenous urogram showed non-function on the right (this kidney had been normal 2 years previously) with poor function on the left. A Hypaque enema showed no reflux or filling defect. Accordingly, it was felt that blockage of her ureters from a cicatricial process was present and exploratory laparotomy was indicated (W.W.H.). On feeling a hard mass where the right ureter entered the colon the bowel was opened and the entire area excised with the distal ureter and a generous segment of surrounding tissue. Frozen section revealed adenocarcinoma which was subsequently confirmed. A similar procedure was carried out at the site of the left ureteric opening, although no gross tumour was present on this side. The colon was closed and both ureters were reanastomosed into the more proximal sigmoid by the combined technique of Leadbetter. Her condition was excellent at the end of 6 months.

Review of Reported Cases

Hammer (1929), is credited with first reporting malignancy after diversion of urine to the intact colon when he described the findings at autopsy in a male who at 40 years of age had undergone a Maydl type operation for exstrophy. Ten years later death ensued with both bowel and uraemic symptoms. A post-mortem examination disclosed a sessile tumour originating from the vesical trigone which had been transposed to the bowel. Histologically it was of a colloid pattern which Hammer felt represented a malignant transformation of the residual mucosa of the exstrophic bladder rather than an origin from the bowel lining.

Nineteen years elapsed before another case of cancer after ureterosigmoidostomy appeared in the literature. Dixon and Weismann (1948) described a patient who had undergone a Coffey type operation at 3 years of age for exstrophy. Some 30 years later, at the time of nephrectomy for a damaged left kidney, colonic polyps at the ureteric anastomotic site were found. After removal by open colotomy one showed adenocarcinoma. In this paper the authors pointed out that transplantation of the ureters individually to the intact colon utilising the valve principle of Coffey (1911) had been accepted favourably by surgeons and was being performed more and more often. As a result longer survival of a greater number of patients could be anticipated. Hence they advocated thorough proctoscopic and roentgenographic studies of the distal bowel in later years after an apparently successful outcome of the diversion. In the last 30 years reports of neoplasm of the colon following ureterocolic anastomosis recognised only after prolonged latency have increased steadily until by 1979 we have been able to tabulate data on a total of 55 such cases.

Table 1 Indications for Ureterosigmoidostomy Followed by Tumour in 55 Patients

Condition	*No. of patients*
Cancer of bladder	9
Benign	
Exstrophy	35
Other non-malignant	11
Total	55

Table 2 Case Reports of Tumours of Colon Developing After Ureterosigmoidostomy for Exstrophy

1929	Hammer
1948	Dixon and Weismann
1961	Aldis
1962	Sugg
1966	Urdanetta *et al.*
1966	Kozak *et al.*
1966	Markowitz and Koontz (3 patients)
1967	Richter and Ginsberg
1970	Oetjen *et al.*
1971	Whitaker *et al.* (2 patients)
1971	Haney and McGarify
1972	Brekkan *et al.* (3 patients)
1973	Mueller and Thornbury
1973	Meyers
1973	Lein
1973	Tank *et al.*
1974	Shapiro *et al.*
1975	Rivard *et al.*
1975	Lasser and Acosta
1975	Harguindey *et al.*
1976	Carswell *et al.*
1976	Besancenez *et al.*
1977	Potet *et al.* (2 patients)
1977	Parsons *et al.* (2 patients)
1977	Mogg

The reasons for the original ureterosigmoidostomy in the 55 recorded cases are shown in Table 1, where it is seen that the initial problem was benign 5 times as often as it was malignant. In the benign category exstrophy was by far the

Table 3 Age and Time Factors in 35 Patients With Exstrophy Who Developed Tumour of the Colon

	Mean in years
Age at time of ureterosigmoidostomy Range: 3 months to 40 years	4
Age at time tumour of colon diagnosed (Youngest 15 years; oldest 57 years)	30
Period of latency from initial ureterosigmoidostomy to diagnosis of tumour Shortest 10 years; longest 46 years	25
(Sex male 21; female 12; not given 2)	

Table 4 Pathological Diagnosis

		No. of patients
Malignant		28
Adenocarcinoma	24	
Other forms of cancer	4	
Benign colonic growths		7
Total		35

predominant indication, and it is these data with which we are concerned hereafter in this communication. A chronological listing of the reported cases is seen in Table 2.

Table 3 shows the data relating to age factors. The mean age at the time of the original ureterosigmoidostomy was 4 years, while that at the time of diagnosis of the colonic lesion was 30 years. The prolonged interval which elapsed between the initial ureterosigmoidostomy and the diagnosis of the neoplasm of the bowel (both the average and the mean being 25 years) was noteworthy.

Table 4 shows the types of lesion which developed in the colon. There the growth was malignant 4 times as often as it was benign. Adenocarcinoma was by far the most frequently occurring histological form characterised as mucinous, polypoid, papillary, colloid or simply "of colonic origin". The non-malignant tumours were described as adenomatous, juvenile or benign polyps. Both types of tumour were multiple on occasions and occurred together at times. Metastases were noted in one-half of those patients in whom the bowel lesion was malignant.

The surgical treatment of the bowel lesion is shown in Table 5. Resection of the sigmoid was performed most often when malignancy was known or suspected, although in a few cases local excision was deemed adequate. Various methods, either alone or in combination, were used for the secondary diversion as seen in Table 6. Surprisingly, repeat ureterosigmoidostomy was the method of diversion employed most often after extirpation of the growth. The original anastomosis was retained in 6 patients and reimplantation into a new site in the bowel was chosen in 14. Nevertheless, recurrent tumour developed at the new site in only one of the latter group (Urdanetta *et al.*, 1966). A kidney required prior or simultaneous removal in 13 (one-third) of the total number of patients. Particularly significant is the fact that cancer developed at the original anastomotic site many years after the urine had been completely excluded from the lumen of the sigmoid in several instances (see below). This emphasises the importance of complete removal of the ureteric stump and the tissue surrounding the orifice, should either a nephrectomy or secondary diversion become necessary.

Table 5 Treatment of Bowel Lesion

Bowel resection	21*
Local excision	7
Via proctoscope	1
Inoperable	6

* 3 for recurrence after: treatment via proctoscope 2: local excision 1.

The outcome in the 35 patients disclosed that 14 had died of cancer at the time of report. Sixteen were alive on short-term follow-up and the result in the remainder was not given. The known death rate of 14/35 attests to the seriousness of the condition.

Discussion

Various figures are found on the increased incidence of neoplasia of the sigmoid after ureterosigmoidostomy as compared to its occurrence in the corresponding segment of the population at large. Calculations by Sooriyaarachchi *et al.* (1977) that the risk is 100 times as great seem reasonable. It is apparent also that the duration the ureters have been implanted into the bowel, *i.e.* the age of the ureterocolic anastomosis rather than the age of the patient, determines the risk.

Study of the individual case reports in Table 2 leads us, as it has led others, to believe that there is unquestionably a cause and effect relationship between the operation and the subsequent develop-

Table 6 Secondary Disposition of Ureters in Connection with Operation for Tumour*

	No. of patients
Reimplantation into sigmoid (one or both; one rectal bladder)	14
Ileal conduit (prior to or in conjunction)	9
Original ureterosigmoidostomy unaltered	6
Cutaneous ureterostomy	4
Unilateral ligation	3
Unoperated or not stated	4
Previous or simultaneous nephrectomy	13

* Various combinations were carried out either simultaneously or in sequence.

ment of neoplasm of the colon. Furthermore, the evidence is overwhelming that the ureterocolic junction is the site of predilection for such tumours, both benign and malignant. Nevertheless, the mechanisms involved in the pathogenesis are unclear. At first glance the urine would seem to be at fault as a carcinogenic agent, yet against this simplistic view is the lack of confirmation by experiments with administration of potent carcinogens to dogs with urinary shunts to the bowel (Scott and Boyd, 1953). Clinically also at least 5 patients have developed cancer at the anastomotic site many years after the urine has been diverted away from the colon (Meyers, 1973; Shapiro *et al.*, 1974; Rivard *et al.*, 1975; Parsons *et al.*, 1977).

Repeated mechanical trauma about the ureteric openings by the faecal stream has also been proposed as an aetiological factor, as has metaplasia and transformation of the ureteric lining to a glandular type epithelium. The sequential biopsies of the mucosa of the bowel by Sommo and Traverso (1967) suggest alteration in the mucous production by the colonic epithelium as a factor in the histological and chemical changes predisposing to malignant degeneration. More recently, in a brief note, Harguindey *et al.* (1975) point out that many times the normal concentration of sodium and potassium bathe the epithelium of the colon for many years in the patient with a ureterosigmoidostomy and this may play a deleterious role. Suffice it to say that all proposed explanations remain speculative.

Nevertheless, the clinical observations and implications are clear and definite. One must never become complacent in monitoring these patients as the years go by. The possibility of late development of malignancy of the colon is real. This makes contrast study of the large bowel and sigmoidoscopy mandatory in later years in addition to urography and electrolyte determination in the conscientious follow-up of the progressively increasing numbers of long-term survivors in the exstrophy category who have undergone ureterosigmoid diversion. It should be remembered also that colonic loops are coming of age and may not be immune to this risk.

Ureterosigmoidostomy has been looked upon with disfavour by some observers ever since ureteric diversion by the ileal conduit became popular 25 years ago. Nevertheless, it has served us well in a series of patients with exstrophy of the bladder when carefully followed. Despite the recognition of an increasing incidence of subsequent neoplasia of the large bowel, abandonment of the procedure for this indication would seem premature. The message is clear, however, that appropriate measures to detect this newly emerging long delayed complication are essential.

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Ureters that Show both Reflux and Obstruction

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Summary—Eight ureters in 6 male patients have been shown radiographically and dynamically to exhibit both reflux and obstruction. The greater the degree of obstruction the more dilated the upper urinary tract. Reflux may be considerable, but in severely obstructed ureters it may be minimal. Both urologists and radiologists should be aware of this unusual association. When it occurs patients should not be managed conservatively, but should have their ureters reimplanted.

It is well recognised that refluxing ureters may also be obstructed, and conversely that obstructed ureters may allow reflux. The purpose of this paper is to describe a further 8 examples of this association to show how the obstruction can be demonstrated and quantified by pressure flow studies and to offer a possible explanation for this phenomenon.

Patients

Since 1973, 131 patients have been seen with vesicoureteric reflux. An antireflux operation was performed on 75 patients (57%). Eight ureters in 6 of these patients have shown both reflux and obstruction. This represents less than 5% of all patients with reflux.

All 6 patients were male. Five patients were aged between 2 months and 2½ years, and one patient was 23 years old. Two showed the phenomenon bilaterally and the rest were equally left and right ureters. The 23-year-old patient presented with lifelong nocturnal enuresis and was found to have bladder instability. The 5 boys presented with urinary tract infections or failure to thrive. One boy had an occult neuropathic bladder, but otherwise there was no associated urological problem in these patients and, in particular, no outflow obstruction.

Radiological Features

The degree of upper tract dilatation was assessed by intravenous urography. The greater the obstruction of the ureter shown by pressure flow studies, the greater was the ureteric dilatation and the poorer the excretion of contrast medium by the kidneys. The adult's ureter showed minimal dilatation, whilst the boys all had considerable dilatation. There was loss of renal parenchyma and in the severely obstructed ureters the renal outlines could barely be seen on the urogram.

The amount of reflux, assessed by micturating cystourethrography, correlated less well with the degree of obstruction. None of the ureters showed reflux until the bladder was almost full, or emptying. The widest and most severely obstructed ureter showed only minimal reflux at the height of micturition. The timing of the appearance of reflux is illustrated in one boy (J.G.) (Fig. 1), who had bilateral wide ureters, but only the right side was obstructed. The left ureter started to reflux on partial filling of the bladder, but the obstructed right side showed reflux only as the bladder began to contract. All of the ureters were slow to empty after micturition, but this aspect was not specifically studied.

Appearance of the Orifice

The ureters were inspected either endoscopically or at the time of reimplantation. In 6 there was a nipple-like projection of the terminal ureter into the bladder, which was more prominent with the bladder empty and seemed to retract or flatten as the bladder filled (Figs. 2 and 3). In the cases with a nipple there was also a shallow pit above the nipple that became deeper on bladder filling, but it did not have the usual appearance of a paraureteric saccule or diverticulum. Endoscopic ureteric catheterisation was performed easily in one boy with a 3 FG catheter despite the nipple-like appearance. At operation all ureters would

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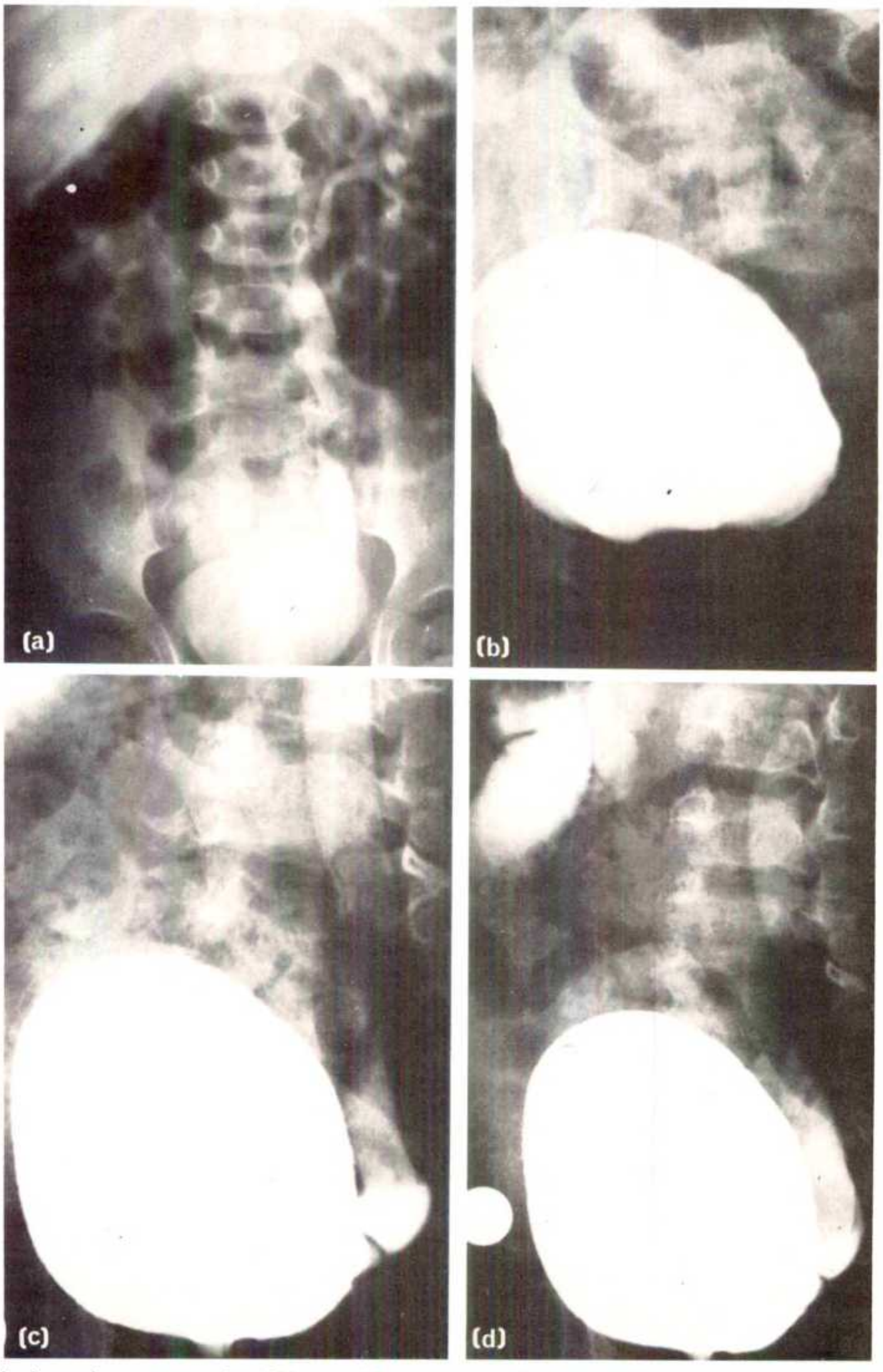


Fig. 1 IVU and micturating cystogram in a 2½-year-old boy (J.G.) (*a*) The IVU shows a grossly dilated right collecting system and poor excretion by the right kidney. The left kidney has normal calices, but there is a wide left ureter. (*b*) The cystogram initially shows no reflux. (*c*) Later, during filling, there is reflux on the left side. (*d*) At the height of filling and the beginning of micturition there is bilateral reflux. Dynamic studies showed that only the right ureter was obstructed.

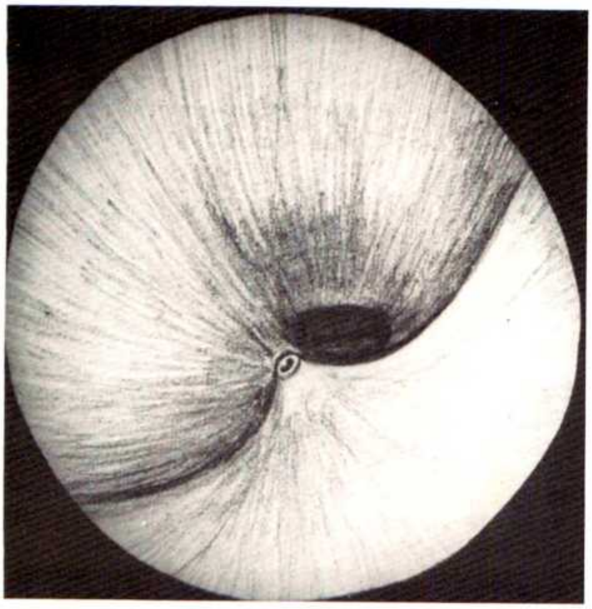


Fig. 2 Appearance of the ureteric orifice both endoscopically and at the time of operation in 6 of the 8 ureters studied.

easily accept a probe and in all there was a direct course through the bladder with no submucosal tunnel. The bladders were otherwise normal in all patients except the boy with an occult neuropathic bladder which was trabeculated.

Dynamic Studies

At the time of operation all of these ureters were occluded as high above the bladder as the wound would allow and the lower end perfused at 10 ml/min with the bladder open (Whitaker, 1973). In one patient a pre-operative antegrade study had also been performed. Such antegrade studies are reserved for those patients in whom the result may alter the clinical management. They were therefore not performed in the remaining 5 patients on whom the decision had already been undertaken to perform ureteric reimplantation.

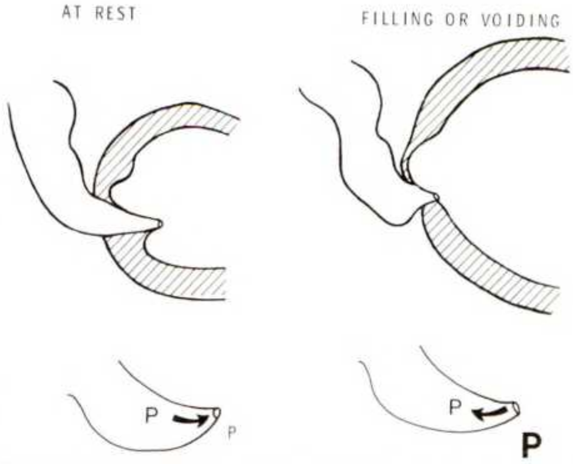


Fig. 3 The nipple-like ureteric orifice is more obvious with the bladder empty. As the bladder fills the nipple retracts. The pressure within the bladder then becomes greater than the pressure in the ureter and reflux occurs.

The pressures were expressed as a pressure drop across the ureteric orifice (relative pressure) (see Table). In one child (P.C.) the pressure was over 100 cm of water at 10 ml/min, so that the results are given at 5 ml/min.

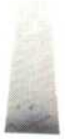
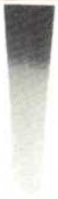
Surgical Management

All 8 ureters were reimplanted, with or without tapering, with a long submucosal tunnel and usually with fixation of the bladder by a psoas hitch. No detailed histological studies were made of the excised lower ureters.

Discussion

As might be expected, the greater the ureteric obstruction the poorer the excretion of contrast medium by the kidney and the more dilated the system. Gross reflux occurred in all patients except the boy with the greatest degree of ureteric obstruction. Reflux always occurred immediately

Table Results of Pressure Flow Studies

Patient	*Side*	*Appearances of orifice*	*Flow rate (ml/min)*	*Relative pressure (cm H_2O)*	*Obstruction*	*Reflux*
D.M.	R	—	10	18		
M.F.	R	Nipple	10	20		
D.P.	L	Nipple	10	28		
M.F.	L	Nipple	10	50		
J.G.	R	Nipple	10	55		
P.C.	L	Nipple	5	21		
P.C.	R	Nipple	5	23		
T.S.	L	—	10	60		

before, or during, voiding and we had the impression that it occurred more readily in those patients with lesser degrees of obstruction. There has been a satisfactory operative result in all 6 patients. Reflux has been abolished, ureteric width diminished and there has been increased excretion of contrast medium from the kidneys.

Weiss and Lytton (1974) described the association of ureteric obstruction and reflux, and Kesavan and Fowler (1977) considered several possible aetiological factors. Although we did not study the anatomy and histology of our patients' ureters in such detail as these authors, we felt that the obstruction was similar to that seen in the idiopathic type of megaureter for which we, amongst others, have already offered an explanation (Whitaker, 1975). A nipple through which a probe could easily be passed was a notable feature in our patients. It suggests to us that the lower end of the ureter is incapable of conducting a peristaltic wave through it into the bladder. The pressure in such an obstructed ureter is constantly raised, but when the bladder is full, or emptying, the bladder pressure exceeds the ureteric pressure (Fig. 3). Because there is no submucosal tunnel, the nipple flattens and the urine is forced back through the orifice into the ureter. Reflux probably occurs as a fine jet which mixes rapidly with the large quantity of urine already in the ureter to give the appearances of gross reflux (Fig. 1).

We agree with Kesavan and Fowler (1977) that these ureters need reimplantation and should probably not be treated conservatively. These authors also performed pressure flow studies in 2 of their 8 ureters and confirmed the presence of obstruction. We found the dynamic studies of considerable interest in this condition. The pressure flow studies showed that the relative pressures were between 18 and 100 cm of water at 10 ml/min. These were in contrast to the results that we have obtained in simple reflux where the pressures have ranged from 2 to 12 cm of water at the same flow rates.

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Minimal Surgical Interference in the Prune Belly Syndrome

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Summary—Twenty-seven cases of prune belly syndrome which were well in the neonatal period are reported. Eleven were seen in the first year of life and 16 presented later. The first line of treatment was to ensure proper bladder emptying, usually by urethrotomy. Thereafter a policy of minimal surgical interference was followed, operating only for proven obstruction and intractable infection. This policy appears justified as 10 of 11 early presenters have done well. In the late presenters it was accepted that some renal damage had already occurred; nonetheless, 11 of 16 cases have done well.

The X-rays were reviewed and hitherto unreported medullary cysts were noted. No radiological signs were found that were of prognostic significance.

There have been regular reports of cases and series of patients with the prune belly syndrome for 140 years. The complete syndrome occurs only in boys and consists of aplasia of the anterior abdominal muscles, bilateral cryptorchidism and complex urinary tract malformations. In an earlier communication it was shown that the syndrome can be conveniently divided into 3 groups according to the clinical severity in the neonatal period (Williams and Parker, 1974):

Group I Complete urethral obstruction leading to neonatal death.

Group II Infant emergency presentation requiring high diversion or total correction of the urinary tract anomalies.

Group III Well in the neonatal period and characterised by good renal function in spite of rather frightening-looking radiology.

Patients

At Great Ormond Street and St Peter's Hospitals we have seen 46 boys, born between 1948 and 1977, with this syndrome. The distribution of the cases is shown in Table 1; 3 cases were unclassifiable because of inadequate information about their early management. In this study we describe the management of the 27 Group III cases which has been based on a policy of minimal surgical interference.

Eleven cases were seen in the first year of life, the remainder being referred at various ages up to 16 years. All patients had urine examination, and haemoglobin, electrolyte and urea estimations, intravenous urograms and micturating cystourethrograms. The plasma creatinine was added in 1966. Particular attention was paid to the outflow tract from the bladder as it was here that a treatable problem was most often found. If there was any doubt a cystourethroscopy was performed. The indications for surgery were intractable infection and proven obstruction.

Treatment

When we have been responsible for the management right from the start, our policy has been to eliminate obstruction in the urinary tract. The first objective was to achieve complete bladder emptying; partial urethral obstruction was found in 6 of 11 boys (Fig. 1). It was treated endo-

Table 1 Distribution of 46 Cases of Prune Belly Syndrome (Patients Born 1948-1977)

Group I	4
Group II	12
Group III	27
Unclassifiable	3

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

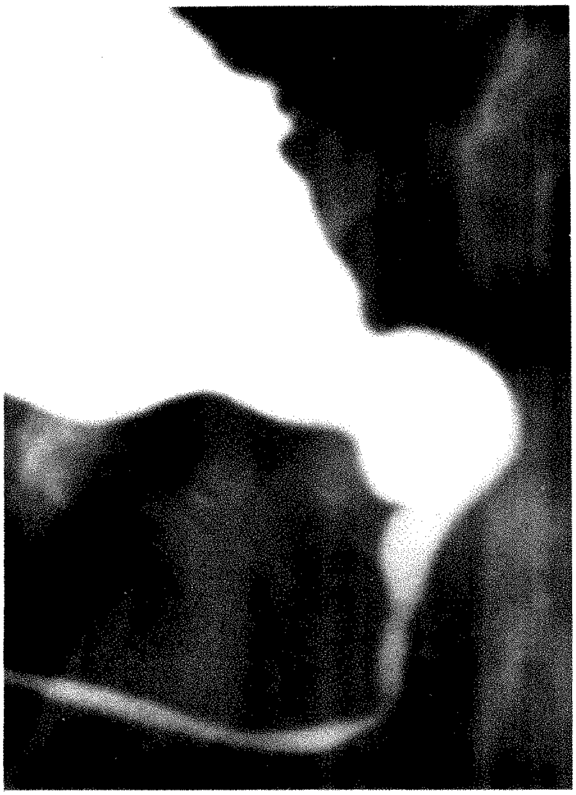

Fig. 1 Micturating cystourethrogram in prune belly syndrome showing the widely dilated posterior urethra and relatively narrow anterior urethra.

scopically in 5 and by urethroplasty in one. In one boy even a second urethrotomy did not produce proper emptying and so the bladder was plicated.

Upper tract surgery was required in 4 boys. In 2 cases the upper tracts failed to improve with proper bladder emptying. They were found to have vesicoureteric junction obstruction and had bilateral remodelling and reimplantation. In 2 others non-functioning and infected kidneys were removed.

In 4 boys no surgery was required in the early years of life.

They were then kept under review. The urine was kept sterile with antibiotics, either prophylactically or in courses. Intractable infection was an indication for further investigation. If a ureter required surgery the testicle was brought down at the same time. Otherwise orchiopexy was performed electively when it had become clear that ureteric surgery would not be needed.

Two boys who had had no early surgery later showed a rise in plasma urea and increasing ureteric dilatation. They were treated by urethrotomy with considerable improvement in the radiological appearances and return of the urea to normal.

Table 2 Upper Urinary Tract Surgery in 16 Boys Presenting Late With the Prune Belly Syndrome

	No. of cases
Nephroureterectomy	2
Bilateral reimplantation of ureters with remodelling	2
Unilateral reimplantation of ureter	1
Remodelling of ureter	1
Pyeloplasty	1
Pyeloplasty, followed by remodelling and reimplantation	1
No upper tract surgery	8

The 16 boys who came to this unit later in life presented a different problem. Their early treatment had been variable; 3 had had procedures to improve bladder emptying and 13 had had no surgery. In general their radiological appearances were worse than in our early presenters and their renal function less good (though only 2 had a plasma urea above 6 μmol per litre).

The principles of management were the same, but it was accepted that some degree of renal damage had already occurred and that ureteric surgery would be hazardous. In 11 boys the urethra was partially obstructed; all were treated endoscopically and one boy had a partial cystectomy. When proper bladder drainage had been achieved, the upper tracts were reconsidered but surgery was avoided if possible. The operations are shown in Table 2.

Early in the series 3 boys had abdominal wall plication. However, it did little to improve the function or appearance of the abdominal wall and has not been performed recently. The pucker-

Table 3 Follow-up of 27 Cases of Prune Belly Syndrome (Patients Born 1948-1977)

	No. of cases	
	Early presenters	*Late presenters*
Remain well Normal micturition Little or no urinary infection Normal urea and creatinine	9	11
Doing badly	1	5
Lost to follow-up	1	
Totals	11	16

ing of the abdominal skin that is so characteristic of this syndrome becomes less marked as the boy grows and is replaced by a premature "beer-belly".

Results (Table 3)

Referred in the First Year of Life

The 11 boys in this group are now aged between 2 and 24 years. One was lost to follow-up at the age of 15, until which time he had been well and had normal renal function. A further boy was lost to follow-up at the age of 2 years, shortly after his initial urethral surgery. It seems clear that his bladder never emptied properly and he went into chronic retention with renal failure. He re-presented at the age of 7 with a plasma urea of 12 μmol per litre and has been diverted by cutaneous ureterostomy.

Nine boys remain well, have normal micturition and little or no urinary infection. Urea and creatinine are normal.

Late Referral

Eleven out of 16 in this group have done well. Six are now over 15 years old and show no sign of further deterioration in renal function. In all who have done well satisfactory bladder emptying was eventually achieved with urethral surgery.

Five boys have done badly for various reasons. One boy had a respiratory arrest shortly after a nephrectomy and has severe brain damage. This is the only anaesthetic problem that we have had.

Two boys have become hypertensive, one at the age of 8 and the other at 20. A third has developed renal calculi and severe psychiatric problems; he is our oldest patient at the age of 31. In all 3 there has been some deterioration in renal function, though the creatinine remains within normal limits in 2 and is 170 μmol per litre in the older hypertensive.

Only one boy, now aged 18, is approaching end-stage renal failure and has a creatinine of 530 μmol per litre. Both his kidneys were severely dysplastic and scarred on presentation and his function was never very good. His bladder emptying was improved by 3 urethrotomies, a dilatation and a bladder plication but was never really satisfactory. No other site of obstruction was found and he rarely had urinary infection. A decision about dialysis and transplantation must soon be made.

Table 4 Details of 6 Cases of Prune Belly Syndrome Who Have Done Badly

	No. of cases
Early presenters	
Chronic retention and early renal failure requiring diversion	1
Late presenters	
Hypertensive	2
Renal calculi and psychiatric problems	1
End stage renal failure	1
Post-operative respiratory arrest leading to brain damage	1

The details of all boys who have done badly are shown in Table 4.

In spite of urethrotomies and other urethral and bladder neck surgery, incontinence has not been a problem. Only one boy was incontinent in childhood; he had a spastic external sphincter incised at the age of 6. Control developed spontaneously at the age of 18. The boy who was diverted at the age of 7 had not achieved continence.

Radiology

The complete X-rays were available for review in only 18 boys. There were 31 functioning kidneys. The appearances of the urinary tract in the prune belly syndrome have been well described by other authors (Berdon *et al.*, 1977). However, we have noted a feature that we believe has not been described before: in 3 cases there were cysts in the medulla which, on intravenous urography, filled with contrast early, certainly before the calices and in at least one case before the collecting tubules. We believe that they are cysts of the

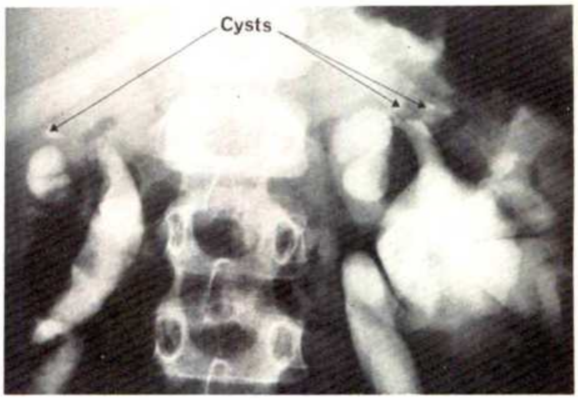

Fig. 2 Intravenous urogram of a boy with prune belly syndrome showing bilateral cysts of the proximal collecting tubules.

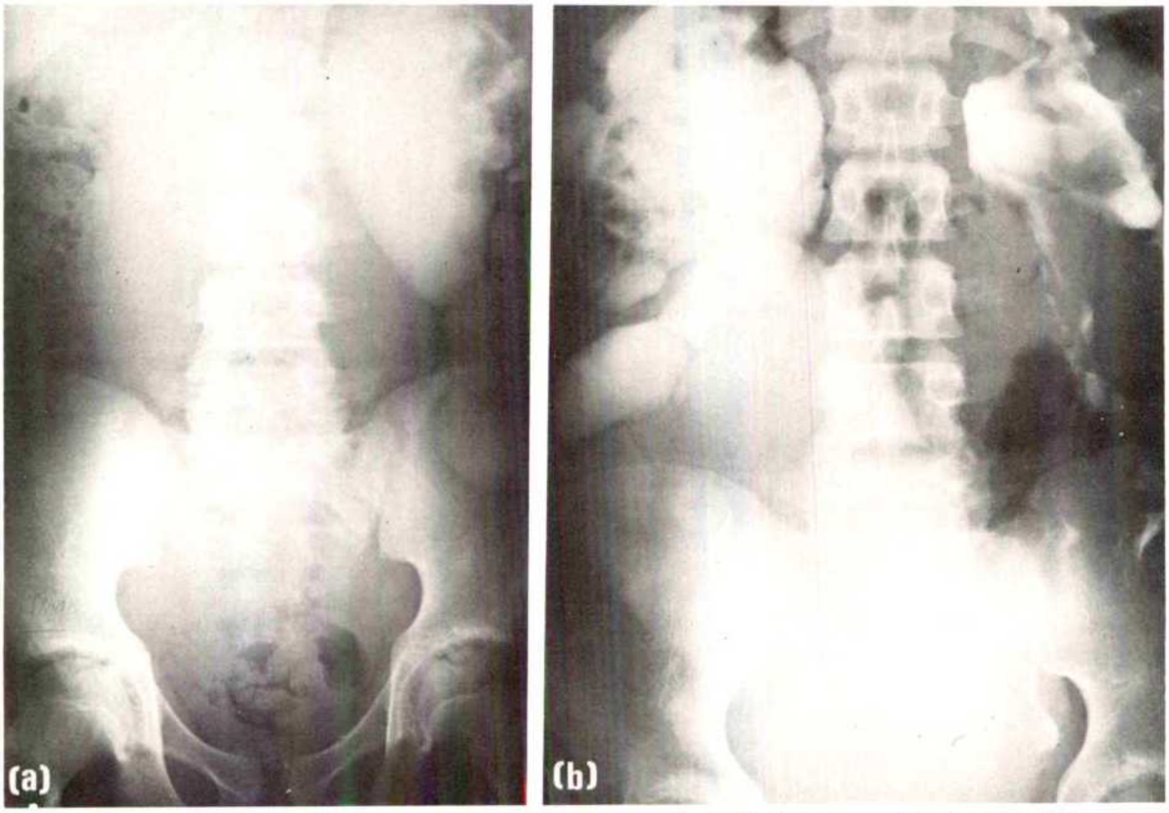

Fig. 3 (*a*) Intravenous urogram before urethrotomy showing poor excretion on both sides, especially the right. (*b*) Intravenous urogram 6 months after urethrotomy showing collapse of the left collecting system and considerably improved excretion on the right. The bladder is still huge but was able to empty normally.

proximal part of the collecting tubules but their significance is not clear (Fig. 2).

No feature could usefully single out boys who were destined to do badly, though 2 features may be pointers. Two boys had parenchymal scars and they both did badly, one becoming hypertensive and the other going into end-stage renal failure. Seven boys had dilatation of the calices and 4 have done badly, while 2 of the other 3 are under 6 years old and are too young to be sure of yet.

Successful relief of bladder outflow obstruction produced marked improvement in emptying, although the bladders remained large. Films were available only in 12 cases before and after such surgery and in 6 the upper tracts were improved (Fig. 3(a) and (b)).

In only one of 3 boys for whom there are full sets of X-rays were the upper tracts improved by reimplantation of the ureters, and he was in the early presentation group.

Renal growth occurred in unobstructed kidneys providing there was reasonable function to begin with. Kidneys showing little or no radiographic function, with poor growth and especially with infection, were removed.

Discussion

The management of the urinary tract abnormalities in the prune belly syndrome is controversial. Some surgeons advocate an aggressive approach, aiming for complete correction of the abnormalities (Waldbaum and Marshall, 1970; Welch and Kearney, 1974; Woodard and Parrott, 1978), while others prefer a more conservative attitude (Williams and Burkholder, 1967; Palmer and Tesluk, 1974; Williams and Parker, 1974). In the Group II patients who present as neonatal emergencies, a good case can be made for total correction of the genitourinary anomalies (Hendren, 1972). In the Group III patients, however, we have found that the general and urological outlook is good with a conservative surgical approach.

In this series of 27 patients there have been no deaths, 20 are completely well and even amongst those that have done badly, only 3 are unable to live a normal life.

In the patients who presented early and were followed up, we have been able to maintain renal function by ensuring proper bladder emptying. Constant vigilance is required as urethral obstruction may recur or present for the first time later in childhood and can be reversed by urethrotomy.

The removal of poorly functioning and chronically infected kidneys has produced an improvement in general health and a reduction in urinary infections. Other upper tract surgery has been less often indicated and has not been as rewarding. Reimplantation of an obstructed ureter, if done early enough, may save a kidney from obstructive atrophy but only in one case has it improved the radiological appearances of the kidneys. We have found no evidence that remodelling improves the function of the ureter.

The cases that presented later in childhood without having had urethral surgery had usually suffered some renal damage. However, it was partly reversible when bladder emptying was improved. Upper tract surgery did not have the same effect.

When an obstructive lesion is present, by far the commonest site is the bladder outlet and urethra. The bladder neck and the posterior urethra are usually dilated, perhaps because of prostatic malformation (Nunn and Stephens, 1961), though in 4 cases bladder neck resection has been required. It is a moot point whether or not the urethra is truly obstructed; in some cases definite areas or rings of narrowing were seen, but in most the normal calibre urethra appeared to produce more resistance than the weak detrusor could overcome. The term "functional obstruction" seems appropriate (Perlmutter and Retik, 1970). Localised strictures were incised but otherwise a full length urethrotomy was performed.

Only 12 of our 27 cases are 15 years old or more and, therefore, past their main pubertal growth spurt. It might be suggested that kidneys that were adequate in childhood would start to fail in puberty. This does not seem to be the case. Amongst our patients with renal complications only 3 began to go wrong as teenagers. We have not witnessed a gradual deterioration of the renal function. It would seem that the condition remains static over many years providing that obstruction is relieved and infection treated.

The intra-abdominal testis in this syndrome is grossly normal. It is now our policy to attempt orchiopexy in all cases. It is usually necessary to divide the testicular artery and to rely on the artery to the vas. For this reason only one side is done at a time. Reasonable pubertal development occurs but none of our boys has fathered a child.

The radiographic appearances are very variable. In general 2 poorly excreting kidneys carried a poor prognosis but we were often surprised by the good function produced by a bad-looking kidney. In managing these patients we have relied heavily on the intravenous urogram and the micturating cystourethrogram. These are notoriously unreliable in assessing obstruction. Nor have we found that urodynamics are of value. It may be that radionuclide and ultrasound studies will provide more accurate information in the future. The non-invasive technique of ultrasound may be repeated to follow-up the dilated collecting systems and ureters.

It is concluded that the boy with the prune belly syndrome who is well in the neonatal period has a good prognosis. Surgery should be carried out only for the relief of obstruction and the eradication of infection. If there is any doubt about the ability of the bladder to empty, urethrotomy should be performed. Three-quarters of our 27 patients have done well with minimal surgical interference.

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Duplications of the Lower Urinary Tract in Children

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Summary—Seven cases of bladder duplication are described, and compared with 27 cases of urethral duplication. Bladder duplication was collateral while urethral duplication was usually in the sagittal plane. The conditions may coexist when the duplication of the bladder extends caudally to produce a collateral urethral duplication, but in one boy bladder duplication was associated with 4 urethrae in the sagittal plane.

In 5 cases the bladders were united; in 2 cases, one bladder was excised. The results were satisfactory in 6 and in one the bladder failed to empty.

The basic defects that lead to duplication are unknown. Several features of the conditions suggest that there are different aetiologies in each type. There are similarities with the exstrophy epispadias complex. Even when there are major abnormalities in other systems the general and urological prognosis is good.

The double urethra, which appears as an isolated phenomenon only in the male, is commonly a duplication in the sagittal plane; double bladder in its ordinary form is a collateral duplication, the 2 organs lying side by side. The difference appears to be fundamental: the sagittal duplication must presumably result from a defect in the midline coaptation of laterally developed structures. In some this represents a variant of the exstrophy epispadias deformity, where the mesodermal structures fail, in their normal inward migration, to separate the 2 primitive layers of cloacal membrane, ultimately to form the anterior abdominal wall and the genital tubercle. In some there is a failure in the closure of the urethral folds which form the tubular urethra out of an open groove.

In the collateral duplication of the bladder and occasionally of the urethra, 2 more or less complete organs are developed, one on either side of the midline. This paper, recording 7 cases of double bladder, draws attention to the fact that the 2 forms of duplication may coexist, most often in relation to the exstrophy deformity, but one remarkable case is described in which a boy presented with collateral duplication of the bladder associated with 4 urethrae in the sagittal plane.

Five varieties of male urethral duplication are recognised and in each case there is a urethra in the normal anatomical position and another, which may or may not be complete, in an ectopic position. In an earlier paper the variations have been classified according to the position of the ectopic urethra (Williams and Kenawi, 1975). If the ectopic urethra is in the penis dorsal to the corpora it is described as epispadiac (Fig. 1), and if ventral, as hypospadiac (Fig. 2). The spindle duplication may be considered as a "dual-carriageway" for part of the urethra (Fig. 3). In the Y-duplication the ectopic limb opens just inside or just outside the anus (Fig. 4). In the collateral (Fig. 5) they lie side by side, often with a partial duplication of the penis. The classification is shown in Table 1.

Duplication of the Bladder (Table 2)

We have seen 7 cases of bladder duplication. In all the bladders lay side by side, separated by a

Table 1 Classification of Male Urethral Duplications

Sagittal duplication

Y-duplication: pre-anal or perineal accessory channel.
Spindle urethra: urethra splits into two and then re-unites
Epispadiac: dorsal penile accessory urethra
Hypospadiac: both urethrae ventral to corpora

- Complete: 2 channels leave the bladder separately
- Incomplete: urethra divides below the bladder
- Abortive: accessory urethra is a blind sinus

Collateral duplication

- Complete with diphallus
- Abortive: one urethra being a blind sinus

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

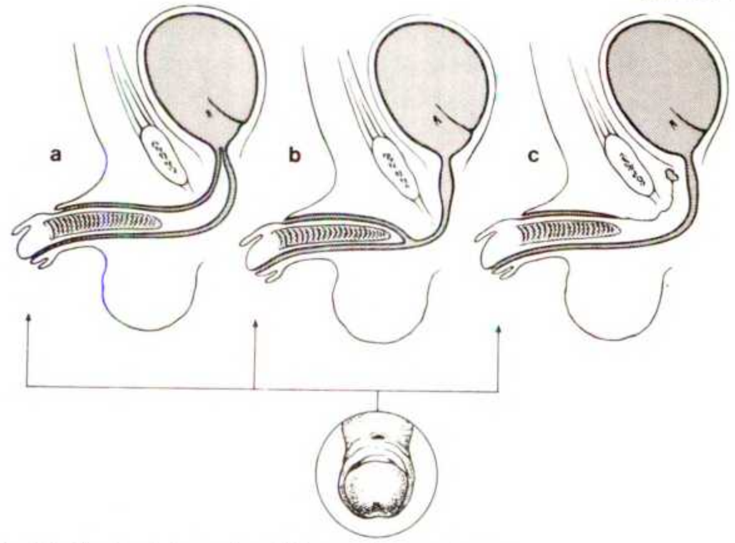

Fig. 1 Epispadiac urethral duplication (*a*) complete (*b*) incomplete (*c*) abortive.

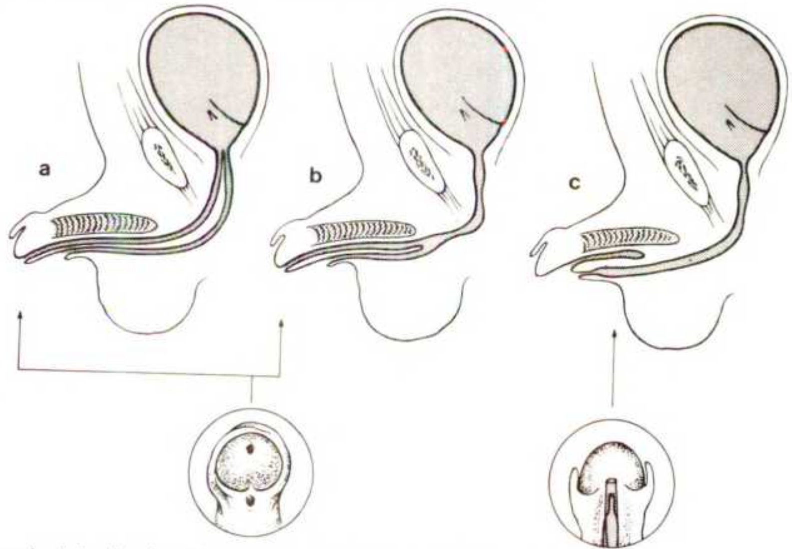

Fig. 2 Hypospadiac urethral duplication (*a*) complete (*b*) incomplete (*c*) abortive.

Table 2 Details of 7 Cases of Bladder Duplication

Case No.	*Initials*	*Sex*	*Bladders*		*Urethrae*	
			Right	*Left*	*Right*	*Left*
1	M.W.	F		Closed	Normal	Atretic
2	J.O'C.	M			Y-duplication	Complete hypospadiac duplication
3	P.L.	M	Small		Single	
4	P.K.	F		Closed	Normal	Atretic
5	D.J.	F			Short and narrow (collateral duplication) Bifid clitoris	Normal
6	L.H.	F			Normal (collateral duplication)	Normal
7	M.A.	F		Ectopia	Normal (collateral duplication)	Epispadiac

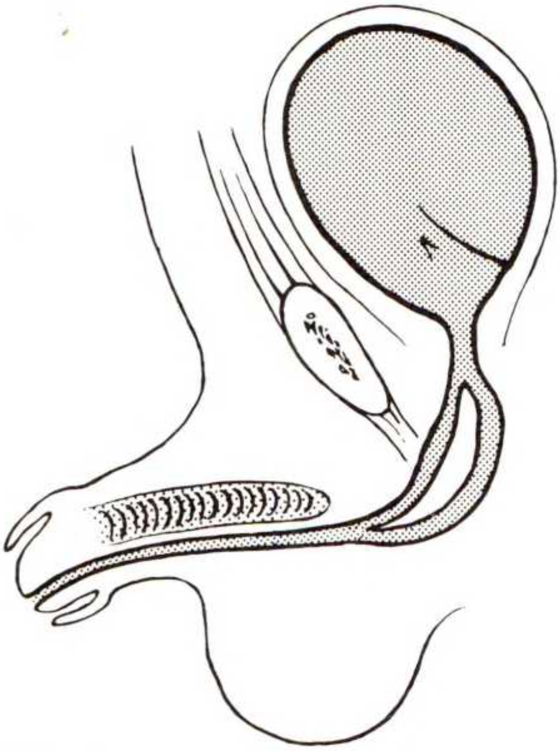

Fig. 3 Spindle duplication of the urethra.

muscular septum (Fig. 6). Each had half a trigone and its own ureteric orifice. Other major genito-urinary abnormalities were present in 6 cases. Four had abnormalities in other systems as well, particularly the spine (Tables 3 and 4).

The outflow tract from the bladders in these cases is of particular interest. There were 5 girls and in 2 of them the left bladder was completely closed off due to urethral atresia; the left kidney was absent in one and non-functional in the other.

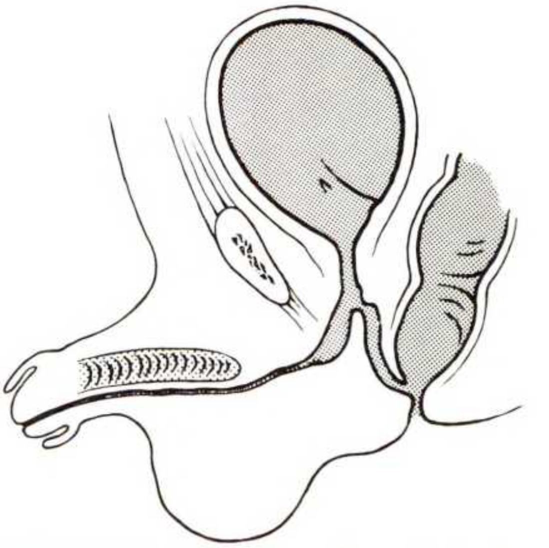

Fig. 4 Y-duplication of the urethra. The accessory track may open just inside or just outside the anus.

In the other 3 the duplication had continued caudally so that there was collateral duplication of the urethra as well.

In one female case the left bladder had ectopia vesicae with a rudimentary epispadiac urethra. The right bladder was covered over and had a narrow urethra. Two other cases had wide separation of the symphysis pubis, suggesting that they might be variations of the exstrophy complex. Such a possibility was reinforced by the finding in case 5 that one of the urethrae was short and narrow.

The male cases had a different arrangement. In one (case 3) the septum had a small defect caudally so that both bladders emptied through a single, normal urethra (Fig. 7).

Table 3 Genito-Urinary Abnormalities in 7 Cases of Bladder Duplication

Case No.	*Sex*	*Kidneys and ureter*	*Testes*	
			Vas	*Vagina*
1	F	Left renal agenesis		Recto-vaginal fistula
2	M	Dysplastic kidneys Bilat. hydronephrosis and hydroureter	Right testis absent Reflux to right vas Left hydrocele	
3	M	Right reflux	Reflux to right vas	
4	F	Non-functioning left kidney Bilat. megaureters		
5	F	Left obstructed megaureter Right dysplastic with reflux		
6	F	Right duplex Bilat. reflux		Double
7	F	None		

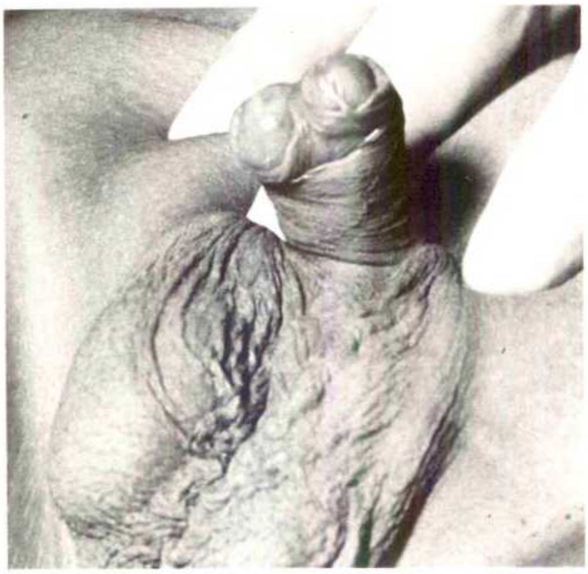

Fig. 5 Partial duplication of the penis.

The most remarkable boy in this series had 2 bladders and 4 urethrae. He was born with several congenital defects (Table 5). The dysplastic right kidney was removed in infancy. He was fully continent but passed most of his urine per rectum and only a little from his penis (the classical symptom of Y-duplication). He sought treatment only at the age of 12.

On examination he was a normally grown boy, well into puberty, with the stigmata of his many congenital abnormalities. The penis was rotated through 90° to the right, and retraction of the normal foreskin revealed 3 external urinary meati close to the normal position.

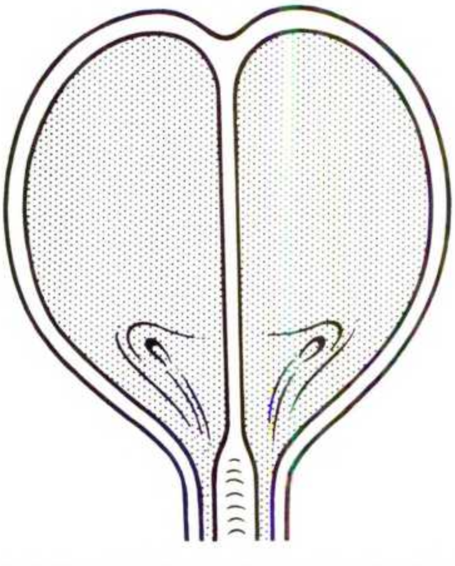

Fig. 6 Collateral bladder duplication. The bladders lie side by side separated by a muscular septum; each has its own ureteric orifice and half the trigone.

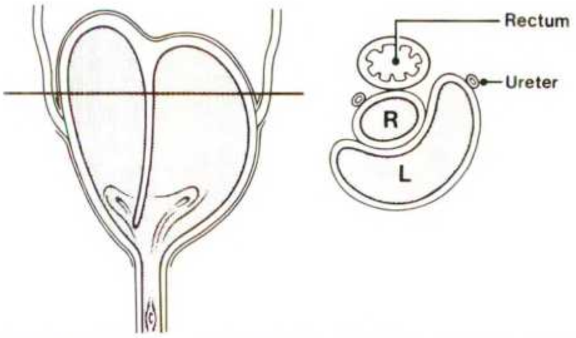

Fig. 7 Bladder duplication in case 3 with a transverse section at the level indicated. The left bladder was larger than and partly enclosing the right bladder. The urethra was single.

Investigation showed that he had 2 bladders separated by a sagittal septum, each with a ureteric orifice. The right bladder had a Y-duplication of its urethra and the left had a complete hypospadiac duplication. The bladders had a small communication just below the bladder neck so that, although the right kidney had been removed, urine could pass into both bladders and through all urethrae (Fig. 8).

Management (Table 6) The aim in managing these patients has been to eliminate stasis by uniting the bladders. In one case the septum was incised and in 4 it was excised; in all 5 a bladder of good size, normal emptying and full continence

Table 4 Non-Urological Abnormalities in 7 Cases of Bladder Duplication

Case No.	*Sex*	*Orthopaedic*	*Other*
1	F	Supernumary left thumb Fused vertebrae L5/S1	Imperforate anus Pyloric stenosis
2	M	Partial fusion L1/L2 vertebrae Hemivertebra at S1 Deformity of feet	Cleft palate Anal stenosis
4	F	Hemivertebra at T12 Sacralisation of L5 Absent coccyx Abnormal sacrum Left leg 1 in short	
6	F		Double appendix Gastro-oesophageal reflux

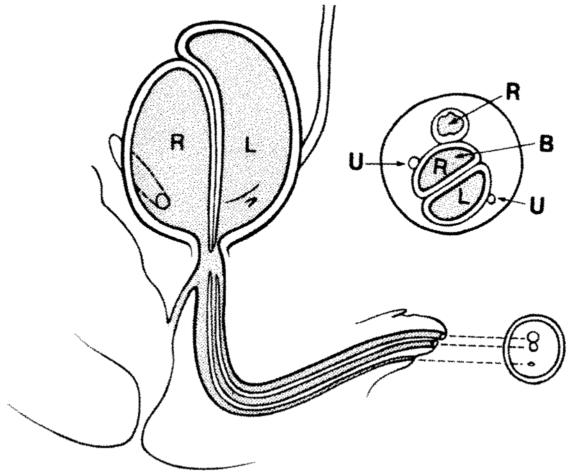

Fig. 8 Diagram of the anatomy in case 2 with collateral bladder duplication and 4 urethrae in the sagittal plane. Inset shows a transverse section, bold initials: U = ureter, R = rectum, B = bladder.

Table 6 Operations Performed in 7 Cases of Bladder Duplication

Case No.	*Operation*	*Result*
1	Incision of septum	Continent with imipramine
2	Excision of septum	Continent
3	Excision of small right bladder and re-implantation of ureter	Continent
4	Drainage of left pyocystis Excision of septum	Died in uraemia
5	Excision of septum and bladder neck reconstruction	Continent
6	Excision of septum and bladder neck reconstruction	Continent
7	Partial excision of open left bladder and septum Cutaneous ureterostomies	Chronic retention and overflow

was produced. Unfortunately one of them (case 4) had only one very dysplastic kidney and later died in uraemia.

In the girl with ectopia vesicae (case 7), the open left bladder was partly excised along with the septum. The remaining defect was then closed. Unfortunately this bladder failed to empty and she was eventually diverted.

Case 3 had a right bladder that was much smaller than the left and so was excised. The right ureter was then reimplanted into the left bladder. He remains well and is fully continent.

Urethral duplications (Table 7)

Three of the cases of double bladder had collateral duplications of their urethrae. Collateral duplication of the urethra can occur with a normal bladder and we have seen 2 cases. Neither was associated with other major abnormalities (Williams and Kenawi, 1975).

Table 5 Congenital Abnormalities in a Boy With Double Bladder and Quadruplicate Urethra

Genito-urinary	*Orthopaedic*	*Other*
Bilat. dysplastic kidneys	Partial fusion L1/L2 vertebrae	Cleft palate
Bilat. hydroureter	Hemivertebra S1	Anal stenosis
Penis rotated 90°	Deformed feet	
Absent right testis		
Reflux to right vas		
Left hydrocele		

In the other 4 types of duplication (Figs. 1-4) the urethrae lie one behind the other so that the septum dividing them lies in the coronal plane. We have seen 25 cases (Table 7). The Y-duplications had a narrow penile urethra in 8 of 9 cases. There were associated abnormalities elsewhere in the urinary tract in 6 cases (Table 8) and in other systems in 5 (Table 9) (Williams and Bloomberg, 1976). The spindle duplications had urinary tract abnormalities in 2 of 5 cases, one of which also had imperforate anus and Hirschsprung's disease. The epispadiac and hypospadiac duplications, on the other hand, occurred in otherwise normal boys in 9 of 11 cases (Table 10) (Williams and Kenawi, 1975).

It would appear that the sphincter mechanism of the normally placed urethra is not affected and, unlike Melchior (1975), we have not found incontinence a major problem. Two of our patients were diverted in early infancy, a further boy has been lost to follow-up and one boy is

Table 7 Urethral Duplications Great Ormond Street and St Peter's Hospitals (Born 1953-1977)

Y-duplication	9
Epispadiac	9
Hypospadiac	2
Spindle	5
Collateral	2
Total	27

Table 8 Urological Abnormalities in 9 Cases of Y-Duplication of the Urethra

Case No.	*Kidneys and ureters*	*Bladder*	*Scrotum and testes*
1	Right renal agenesis Right ectopic ureter with reflux	Open neck	
2	Bilat. obstructed megaureters		Bilat. cryptorchidism
3	Bilat. reflux		Bifid scrotum
4	None		
5			Bifid scrotum
6		Calculus	
7	Bilat. hydronephrosis Left reflux	Chronic retention	
8	Bilat. reflux Ectopic ureter	Chronic retention	
9	Right reflux with pyelonephritis	Chronic retention Diverticulum	

only 18 months old. The remaining 22 of our 26 survivors have normal continence.

Discussion

Six forms of double bladder have been described (Abrahamson, 1961) but 4 of them are variations of a sagittal septum and all of our cases have been of this type. There has been some dispute about the number of urethrae that occur in this condition (Tacciuoli *et al.*, 1975). We found that in the girls, where there were 2 draining bladders there was a collateral duplication of the urethra. Such an arrangement has also been reported in a boy (Kossow and Morales, 1973). This variation may be regarded as a caudal extension of the duplication. In boys the anatomy may be more complex; we found one case with a single urethra and cases have been reported with partial urethral duplication (Wegenke *et al.*, 1977). Our other boy had 4 urethrae lying one behind another.

The embryology of lower urinary tract duplications is unknown, though several theories have been put forward (Abrahamson, 1961; Williams and Kenawi, 1975; Stephens and Donnellan, 1977). The fact that the plane of the septum in the bladder and collateral duplications is at right angles to that of the other duplications means that the conditions must be of different origin. Other features suggest that even where the plane of the septum is the same the conditions may arise from different basic defects.

Table 9 Non-Urological Abnormalities in 9 Cases of Y-Duplication of the Urethra

Case No.	*Orthopaedic*	*Other*
1		Rectal agenesis
2	Multiple hemivertebrae	Tracheo-oesophageal fistula
3		Right inguinal hernia
6	Sacral agenesis	
8		Tracheo-oesophageal fistula Congenital heart disease

In the Y-duplications the atretic penile urethra suggests that normal development begins, but is interrupted by a vascular accident (Williams and Kenawi, 1975). The rectal limb should then be regarded as a fistula that was formed early enough to have the characteristics of a urethra. This abnormality must not, however, be confused with the rectourethral fistula of imperforate anus, which is a separate problem (Williams and Grant, 1969).

Epispadiac duplication was associated with widening of the symphysis pubis in some of our cases and one also had a deficient bladder neck. Effman *et al.* (1976) have reported similar cases. Such findings suggest that this type of duplication is yet another variation of the exstrophy epispadias complex.

Bladder duplication also has features in common with the exstrophy complex. In the classical cloacal ectopia vesicae the bladder and genital tubercle are formed in 2 parts. One of our cases had one open and one closed bladder and, although it is not common, several similar cases have been reported (Kogan *et al.*, 1976).

The situation is further complicated by the fact that the bladder and Y-duplications nearly always occur with other major congenital abnormalities, while hypospadiac, epispadiac, spindle and collateral duplications usually occur in isolation.

It seems clear, therefore, that many factors are involved in the development of lower urinary tract duplications. The occurrence of duplications in different planes in one boy shows that they are

Table 10 Congenital Abnormalities in 18 Cases of Urethral Duplication (Spindles, Epispadiacs, Hypospadiacs and Collaterals)

	Genito-urinary	*Other*
Spindles		
1 case with	Right reflux Non-functioning left kidney Bilat. cryptorchidism	Imperforate anus Hirschsprung's disease Left congenital dislocation of the hip
1 case with	Bilat. hydronephrosis and hydroureter Anterior urethral diverticulum	
Hypospadiacs		
1 case with		Meconium plug obstruction
Epispadiacs		
1 case with	Incompetent bladder neck	

not mutually exclusive. Our experience has been that even in the presence of other severe congenital abnormalities the general and urological prognosis is good.

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Müllerian Duct Remnants in the Male

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Summary—Persistent remnants of the caudal Müllerian duct in the male may occasionally give rise to symptoms and pose a problem of management. We describe 13 cases which have been seen over a 24-year period. In 4 cases the remnant took the form of a cyst, whilst the other 9 had tubular utricular structures. Not all had an associated maldevelopment of the genitalia and there was no relationship between the size of a tubular remnant and the degree of genital abnormality.

Infection generally appeared to be related to the presence of obstruction to the free drainage of the contents of the remnant, and epididymitis occurred where free reflux into the vasa was present. Apparent incontinence was sometimes the result of urine pooling in the utricular pouch. The radiological demonstration of these structures was not always easy and in our experience voiding cystourethrography was the best means of achieving a diagnosis. Surgical excision of these structures can be difficult, and if they do not produce symptoms they should be left alone.

Vestiges of the Müllerian duct system are to be found in the male and these may occasionally give rise to symptoms. Apart from the relatively straightforward and common problem of torsion of the pedunculated hydatid of Morgagni, incomplete obliteration of the caudal part of the ductal system in the male may give rise to cysts lying between bladder and rectum. Some connect by a narrow track with the posterior urethra. Dilated utricles and tubular vagina-like structures may exist. These generally drain freely into the posterior urethra, but may become obstructed by unsuccessful operations on the anterior urethra.

In this respect it is not intended to review the whole group of hypospadias and intersex cases, in which dilated utricles or tubular vaginal structures are not uncommon, but to discuss only those in which the abnormality produced symptoms. Similarly, in the prune belly disorder a small utricular dilatation is common, but in none has it been identified as responsible for any local disorder.

Patients and Methods

Thirteen symptomatic patients attended the Hospital for Sick Children, Great Ormond Street, or St Peter's Hospitals, London, between the years 1955 and 1979. Age at presentation ranged from 2½ years to 58 years with an average age of 15 years. Eight of the group (61%) were under 10 years of age when first seen.

Symptoms

Dribbling incontinence was a problem in 4 children. All eventually proved to have an unobstructed tubular utricular structure arising from the posterior urethra. One of these children subsequently developed epididymitis after endoscopy.

Three had recurring urinary infections with associated fevers and the passage of blood or pus in their urine. All 3 had evidence of distal obstruction. Two had cystic structures, palpable rectally, which communicated with the posterior urethra and drained slowly on compression. The third had a urethral stricture following an attempted hypospadias repair at another hospital.

Five developed epididymitis. One again had obstruction caused by an iatrogenic urethral stricture. In 2 the epididymitis followed endoscopy. Another had a cystic structure into which both vasa emptied. Although this communicated with the posterior urethra, its drainage appeared obstructed and this man had an extreme oligozoospermia. Two patients presented with difficulty in voiding. One had stones lodged in a tubular remnant, whilst another had a tense Müllerian cyst. Another man with a cyst complained of a deep perineal pain on voiding urine or defaecating.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Physical Examination

In 3 of the 4 cases with cystic remnants it was possible to feel a fluctuant midline swelling on rectal examination. This was situated immediately above the prostate. The stone felt in the dilated utricle could also be felt in this way. In 2 of the 5 cases with epididymitis the vasa and vesicles were palpably thickened.

Eight of the 13 had some degree of hypospadias: 7 of the 9 with tubular structures and only 1 of the 4 with cystic remnants. Six of the former group had maldescent of one or other testicle and 4 had a small penis.

Diagnosis

The diagnosis was confirmed radiologically in 11 of the 12 cases in which X-rays were taken. The intravenous urogram (IVU) failed to demonstrate the remnant on 4 occasions and a urethrogram was either completely unsuccessful or delineated the structure very poorly on 3 other occasions. In each of these cases a micturating cystogram (MCU) was successful in outlining the structure (Fig. 1). Four of the 5 patients with epididymitis had radiological evidence of reflux into the affected epididymis or a dilated utricular remnant.

Seven of the patients were examined by urethroscopy and in 6 of these an opening could be seen in the floor of the posterior urethra in the region of the verumontanum; in the other case the verumontanum was unusually prominent. The stone in the dilated utricle in one patient could be clearly seen.

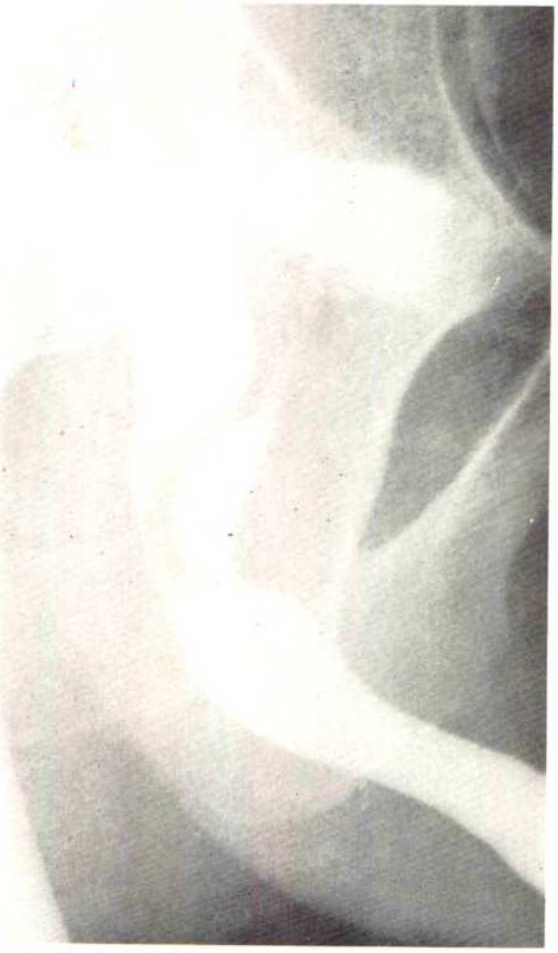

Fig. 1 Cystic Müllerian duct remnant demonstrated by micturating cystourethrography.

Treatment and Results

Treatment and results are summarised in the table.

Three of the 4 incontinent patients underwent an operation to remove a dilated utricular remnant. On 2 occasions this was achieved via a parasacral approach and once via a suprapubic transpentoneal route, mobilising the bladder forwards. All 3 were dry thereafter. The fourth was not operated upon and has been lost to follow-up.

Table Operative Removal: Technique and Results

Structure	*Number*	*Problem*	*Approach*	*Result*
Tubular remnant	3	Incontinence	Parasacral (2) Suprapubic (1)	Dry
Tubular remnant + refluxing vas	1	Epididymitis	Suprapubic	Well
Stone in utricular pouch	1	Difficulty	Transtrigonal	Well (pouch remains)
Utricular cysts	3	Infection Difficulty Pain	Suprapubic	Well

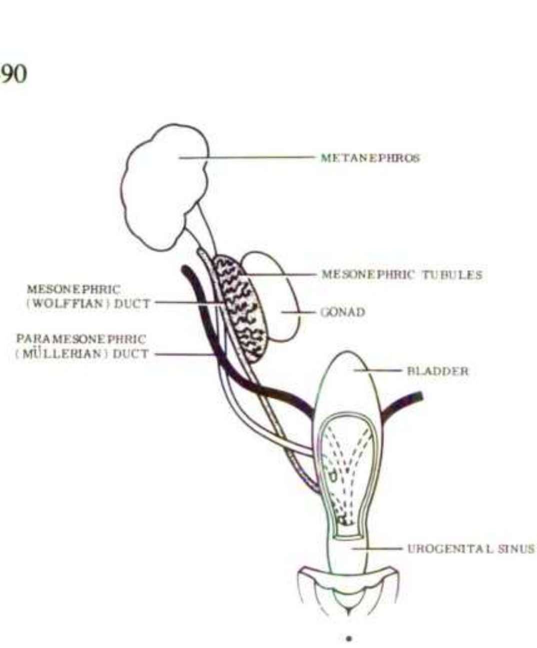

Fig. 2 Embryological development of the genitourinary system at 27 mm stage.

All 3 palpable cysts were removed via the suprapubic approach with relief of their symptoms in each case. One child with recurrent epididymitis had a dilated utricle and reflux into the vas, which entered it. When these strictures were removed the symptoms resolved.

The stones in the utricular diverticulum were eventually removed via a transtrigonal approach. The diverticulum was not excised.

Discussion

The paramesonephric or Müllerian ducts first appear in the human embryo at the 10 mm stage of development as an invagination of the coelomic epithelium into the mesenchyme lateral to the mesonephric ducts. As each increases in length a lumen appears in its upper part which extends towards the growing tip. Each paramesonephric duct eventually crosses in front of the mesonephric duct to meet (at approximately the 28 mm stage) its fellow from the opposite side to form a single tube, the uterovaginal canal (Fig. 2). The caudal tip of this structure then comes into contact with the posterior wall of the urogenital sinus where it produces the elevation of Müller's tubercle.

After the 28 mm stage the paramesonephric ducts regress in the male as a result of the Müllerian inhibiting substance produced by the developing testis (Jost, 1953; Josso *et al.*, 1977). A cranial remnant of the duct commonly persists as the appendix testis and Müller's tubercle remains as the verumontanum. The prostatic utricle has commonly been accepted as the homologue of the female uterus (utriculus masculinus) and thus a derivative of the caudal remnant of the paramesonephric ducts. This view has been challenged, however, and it may be that this structure is, at least in part, derived from the Wolffian duct (Frutiger, 1969) or the cells of the urogenital sinus (Vilas, 1933).

Certainly in intersex cases, where the "utricular" tube takes the form of a vagina, it seems likely that its embryological development would parallel that of the vagina in the female. Despite early claims that the vagina is entirely of Müllerian origin (Bloomfield and Frayer, 1927; Hunter, 1930) it now seems that it derives, in part (Koff, 1933) or in whole (Forsberg, 1963), from the proliferation of cells of the sinovaginal bulbs. These are paired outgrowths of the urogenital sinus which appear at the 63 mm stage of embryonic development. Moore in 1937 presented an embryological study of 678 prostates, showing in all the presence of an atrophic paramesonephric cord traversing the prostate and terminating near the verumontanum. Involution of this cord occurred during the fourth decade.

Englisch (1873) is generally credited with the first description of a Müllerian duct cyst. However, in the previous year Smith of Baltimore had aspirated 5 quarts of grumous fluid from a cyst above the prostate (Smith, 1872) and it is likely that this too was a Müllerian cyst.

Classically these cysts are midline structures,

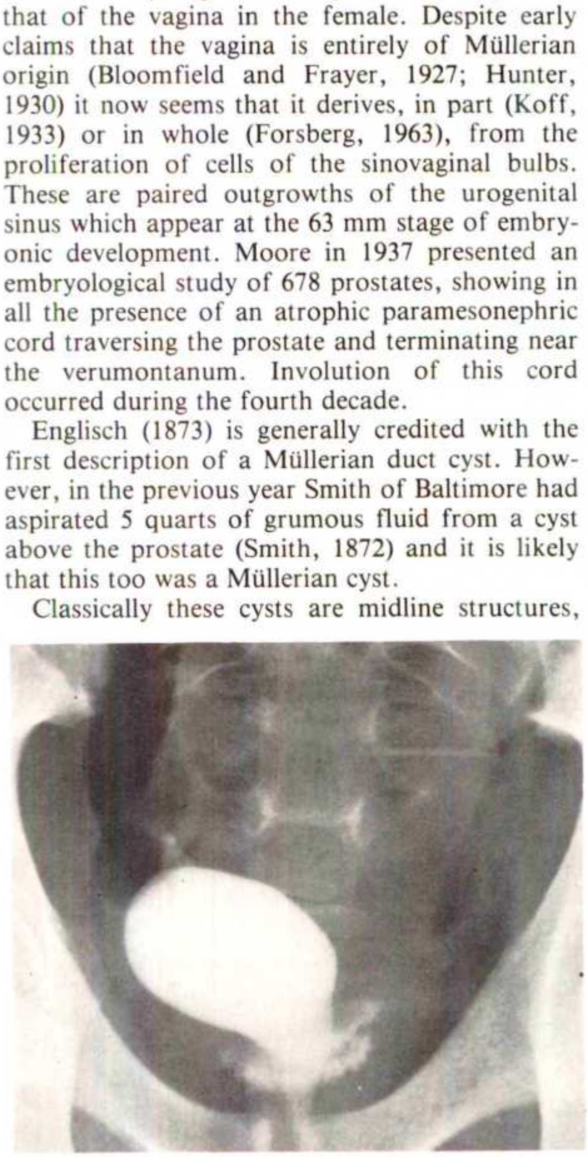

Fig. 3 Cystic remnant drawn over to the right side, possibly due to connection with the right vas.

yet in one of our cases the cyst was found to be pulled over to one side of the midline (Fig. 3), possibly as a result of its connection with the right vas which blended into its wall. In both of the other cases which underwent operation the vasa similarly blended with the wall of the cyst and were possibly damaged during the excision. In 2 patients it seemed that the vasa directly entered the cyst and this has also been more recently reported by other authors (Stanley, 1969; Hassler and Weber, 1978).

Müllerian duct cysts must be differentiated from cysts of the seminal vesicle, ejaculatory duct and prostate and this problem has been well reviewed by Lucey (Lucey *et al.*, 1973). A somewhat similar picture may arise in cases of imperforate anus with a rectourethral fistula which have been treated by reconstructive operations. Here a stump of bowel may be left, forming a diverticulum of the urethra which may occasionally give rise to problems (Williams and Grant, 1969).

Müllerian cysts are characteristically difficult to excise completely as the front wall of the cyst blends with the posterior bladder wall. For this reason some authors have recommended aspirating the cysts or emptying them by massage if a connection with the posterior urethra exists. Either the suprapubic or parasacral approach could be used if excision is to be attempted.

Where the Müllerian remnant persists as a utricular tube, there is often an association with maldevelopment of the genitalia. However, this is not always the case (Stuppler *et al.*, 1973) and 2 of our 9 patients had normal genitalia. Unlike Howard (1948) we have been unable to demonstrate a relationship between the size of the tubular remnant and the degree of genital abnormality.

Enlarged utricles are quite commonly encountered in intersex cases. Most are symptom-free but occasionally urine pools in the structure, emptying slowly after voiding has finished and thus presenting as dribbling incontinence. It seems that where obstruction is present, infection or epididymitis can occur. In our cases where epididymitis was associated with radiological evidence of free reflux into the vasa it seemed that the vasa entered the remnant directly, rather than entering the urethra via the ejaculatory ducts. This abnormal arrangement was certainly familiar to Arnold when he wrote his classical description of enlarged utricles over 100 years ago (McKenna and Kiefer, 1939).

The remnants were not always easy to demonstrate radiologically and both IVUs and ascending urethrograms failed to demonstrate utricular structures where these were present. In our experience a voiding cystourethrogram with dilute contrast medium was the most successful means of demonstrating these pouches.

On urethroscopy the opening of the tubular structure may be clearly visible in the floor of the posterior urethra, either at the region of the verumontanum or just distal to it. In one of our cases, although no distinct opening could be seen, the verumontanum was particularly prominent and a central slit was visible. A micturating cystogram revealed a tubular utricular structure.

It may be that where the tubular remnant is of "vaginal" (*i.e.* sinovaginal bulb) origin the opening will be seen placed distal to the verumontanum.

As in the case of the cysts, excision of the tubular structures is difficult and the surgeon risks damaging the bladder and rectum as well as causing sterility by dividing the vasa. If these structures are not producing symptoms they should be left alone.

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Urinary Incontinence: Prevalence and Needs

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Summary—The prevalence of recognised urinary incontinence in a community was found to be 1%; the prevalence of unrecognised incontinence was 3.3% in men and 8% in women in a group practice of 7000 patients.

The approach to investigation and management of urinary incontinence in a urodynamic unit and the staffing of this unit are described.

Urinary incontinence is a common condition, not merely to the urologist but to clinicians from many other disciplines, and the problem presents a range of morbidity that needs to be considered in broad perspective. An increasing awareness of its prevalence attracts more patients to seek advice, who would otherwise have accepted minor inconvenience as a natural event of life, particularly with advancing age. Many recent studies have stressed the need for objective evaluation of both its pathophysiology and treatment and, on the basis of these, a policy is now required to answer the growing demand for improved care of the incontinent patient within the available health services.

Since 1971 the development of the Urodynamic Unit in Bristol has resulted in over 4000 referrals and the majority of these patients had some degree of urinary incontinence. Their contribution towards clinical research highlighted the necessity to provide early and effective measures that could be undertaken for a distressing disorder rather than a protracted inter-regnum on a waiting list.

Prevalence Study

In order to formulate a rational policy, an estimation of the size of the problem was necessary. A study of the prevalence was undertaken in conjunction with the Epidemiology and Medical Care Unit at Northwick Park Hospital, under the direction of Dr Meade. Such a study requires both a definition and a threshold at which the condition may be considered a problem. The definition chosen for this was the involuntary excretion, or leakage of urine and/or faeces, in inappropriate places and at inappropriate times; the threshold consisted of either dribbling incontinence or 2 or more episodes of incontinence in the previous month and included those patients treated with catheters or appliances.

Two major groups required identification: firstly those patients recognised to be incontinent by the health and social services and secondly, those not recognised by these sources.

The prevalence of recognised incontinence was studied in a population of 37,000, based on 3 health centres. The incontinent patients were reported by the general practitioners or the community nurses and the additional sources included hospitals, elderly people's homes and the social and welfare services; 368 patients were registered by this method during the course of one year, representing 1% of that community.

The prevalence of unrecognised incontinence in the community was undertaken by means of a postal survey in one group practice of about 7,000 patients. A questionnaire was sent to every patient aged 16 years and over and parents were asked to reply for children aged 5 to 15 years. A further 2 questionnaires were sent as reminders, when necessary, and in all 93% of the patients replied. A total of 349 people experienced 2 or more episodes of incontinence per month, or 5.4% of the responders; 3.3% of the men and 8% of the women experienced this degree of incontinence and the majority were identified in the group of women of 65 years and over (Table 1).

These figures were similar to those obtained in a similar survey in Harrow and they have been previously reported (Thomas *et al.*, 1978); 80.7% had urinary incontinence alone, 12.4% had both faecal and urinary incontinence and 7% had only faecal incontinence.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 1 Prevalence Study of Unrecognised Incontinence

Age	*Postal survey*	
	Male incontinent (%)	*Female incontinent (%)*
5-14	6.1	4.4
15-64	2.0	7.6
65 and over	5.7	13.9
Total	3.3	8.0

The population over the age of 5 years in Avon under the Area Health Authority has been estimated at 740,200 (1977). Thus a total of about 7500 patients with incontinence could be anticipated from the survey of recognised incontinence and on the basis of the postal survey of unrecognised incontinence 42,000 might consider that they had some problem with the condition.

Urodynamic Studies

Since 1975, 2290 patients have been referred to the Urodynamic Unit in Bristol for urine-flow studies, cystometry and urethral pressure profile analysis, and these may be considered representative of the clinical service now provided within the Avon Area Health Authority. The value of the computer system for data recording and analysis of any group of patients has been fully substantiated (Wickham *et al.*, 1975). Fifty-four per cent of the men experienced some form of incontinence and of these 85% had either urge incontinence, a post-micturition dribble or enuresis. Seventy-seven per cent of the women were incontinent and 78% of these had either stress incontinence, stress and urge incontinence or urge incontinence alone. Enuresis was a problem in 10% of the women. Continuous conscious or unconscious incontinence affected 10% of the men and 8% of the women (Table 2).

The majority of the men were aged between 60 and 64 years and the majority of the women between 45 to 49 years (Fig.).

Table 2

Types of incontinence	*Male (%)*	*Female (%)*
Stress	2	25
Stress/urge	1	33
Urge	33	20
Enuresis	25	10
Post-mict. dribble	27	1
Continuous	10	8
Uncategorised	2	3

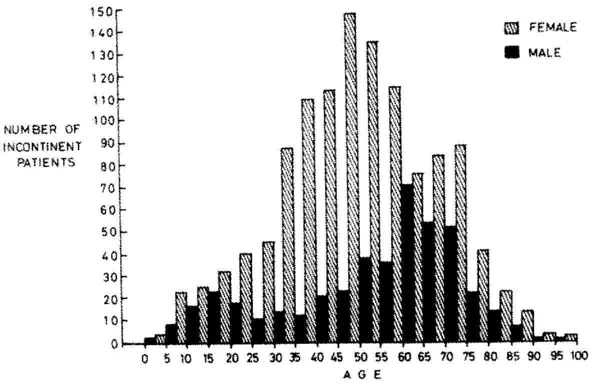

Fig. Age distribution of patients with incontinence.

The grade of urinary incontinence showed a wide disparity. Nearly 50% of the men and only 18% of the women had a minor inconvenience; 42% of the men wet their clothes but only 5% wore any protection, whereas 45% of the women wet their clothes and 36% of them wore some form of padding to control this. Appliances and catheters were required in a small proportion of cases (Table 3).

Clinical Investigation Unit

By tradition, patients are referred to surgical clinics for assessment of incontinence, but this is not always in the patient's best interests. Detailed evaluation is necessary and primary referral to the Clinical Investigation Unit is now encouraged. A careful clinical appraisal is undertaken with the history and examination recorded on computerised data sheets and the emphasis is placed on selective investigations and treatment.

Urodynamic investigations are performed not only on these patients but also on those referred from specialist clinics. A full report is prepared and sent to both the consultant and the general practitioner concerned. Treatment and nursing management of the problems can then be commenced at the time of their first visit to the Unit.

Table 3 Grade of Incontinence

Grade	*Male (%)*	*Female (%)*
Drops	46	18
Wet clothes	42	45
Pads	5	36
Appliance/catheter	7	1

Conservative Treatment

A multi-factorial approach to the unstable bladder has been advocated (Rees *et al.*, 1978) and a greater appreciation of the psychosomatic aspects of the problem of urge incontinence has been recognised (Frewen, 1978). Our experience has substantiated the need for a conservative approach in selected problems.

Drug therapy has an important place, but despite greater understanding of the neuropharmacology of micturition, the results are variable and do not appear to follow any logical pattern. Intensive re-education of the pelvic floor follows the proposition of physiologic therapy for patients with stress incontinence (Kegel, 1951). The use of the perineometer to monitor improved function of the pelvic floor has been confirmed in this group.

Maximum perineal stimulation is based on the treatment described by Moore and Schofield (1967). The use of this in both stress incontinence and urge incontinence is at present under trial in the Unit. Previous pilot studies have shown that up to 30% of the patients receiving this form of electrical stimulation, at the time of cystoscopy under general anaesthesia, have been cured of stress incontinence.

Selected patients require operative treatment and these patients are referred to urologists or gynaecologists. An initial trial of conservative measures is not without advantage in the selection process.

Staffing

The medical staff in the Clinical Investigation Unit consists of 2 Clinical Assistants, both of whom are women, and one Research Registrar. One of the Clinical Assistants holds 9 sessions per week and has a special interest in gynaecological problems, and the other undertakes 4 sessions a week, with a particular experience of the enuretic group of patients. Each Assistant performs 3 urodynamic sessions per week and also undertakes initial assessment and follow-up of patients at the routine clinics in the Urological Department.

The Research Registrar has so far always been male, which conveniently balances the Unit. He undertakes a proportion of the routine service work, but particular emphasis is placed on his special studies for a higher degree.

The Medical Physics Technician maintains the equipment and liaises with the Hospital Medical Physics Department whenever necessary. She prepares the data for the reports and also organises the records for the computer punch cards.

The appointment of a Nursing Sister, as an Incontinence Nurse Adviser, has opened a further dimension to the Unit, particularly with regard to problems in the community care.

A full-time secretary is required to co-ordinate the work of the Unit.

Nursing Management

Patients with urinary incontinence cannot be adequately managed without close co-operation of the nursing staff, both in the hospital and the community. The Incontinence Nurse Adviser (Isaacs, 1979) is particularly involved in the management of the elderly patient and undertakes home visits to assess the patient, the problem and the environmental factors. Selected patients are then referred either to the Unit for out-patient assessment or arrangements are made for a short 5-day stay in hospital.

Despite a certain prejudice, liaison between the hospital and the community nursing staff has been established. Community nurses now visit the Unit for group discussion of particular patients and their problems.

The teaching role of this nurse has focused attention on the care of the incontinent patient, improving the morale of both the patients and the nursing staff.

A wide selection of protective garments, catheters and appliances is now available. Market research on these, with suitable trials, is being undertaken and these have influenced the provision of adequate and suitable supplies for patients, which previously had been restricted.

Research

The place of research in medicine has been summarised by Sir Andrew Kay under the headings of biomedical research, clinical research and research directed towards improving the health services. These comprise a unity which is interdependent and a reasonable balance should be maintained between them. Urodynamic studies have arisen from advances in biomedical techniques and clinical research has established them as part of the routine investigations for the assessment of the majority of patients with urinary incontinence. With a limitation on the available resources, the concept of a Unit to incorporate research, investigations and the clinical management of urinary incontinence has been developed within the Urological Department in Bristol and this experience may have a wider application in the Health Service.

Acknowledgements

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A Comparison of Vaginal and Suprapubic Surgery in the Correction of Incontinence due to Urethral Sphincter Incompetence

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Summary—A preliminary comparison is presented, with pre-operative and post-operative objective assessment, of 25 women undergoing anterior repair and 25 women undergoing colposuspension for the correction of incontinence due to urethral sphincter incompetence.

Colposuspension was found to be more effective. The mechanism of successful cure was likely to be a combination of bladder neck and proximal urethral elevation and narrowing.

By convention, gynaecologists have sought to cure incontinence due to urethral sphincter incompetence by an anterior vaginal repair. This has the additional merit of correcting any coexistent vaginal prolapse. However, there are many reports which doubt the long-term effectiveness of this procedure and advocate suprapubic operations (Hodgkinson, 1970). The major disadvantages of the latter are an inability to correct any anterior vaginal wall prolapse, found in 50% of patients with urethral sphincter incompetence, and a more extensive dissection with a possible increase in morbidity.

We have compared the effect of the anterior vaginal repair with the modified colposuspension operation in patients who complained of stress incontinence with or without prolapse and who were shown by urodynamic investigation to have incontinence due to urethral sphincter incompetence.

Patients and Methods

There were 50 patients in the study. Twenty-five patients underwent anterior repair: in addition 10 had a vaginal hysterectomy and 2 had an amputation of cervix and a posterior repair. Their mean age was 54.8 years (SD 11.4) and parity was 2.1. Three patients had been operated on previously for incontinence. Twenty-five patients underwent colposuspension: in addition 8 had an abdominal hysterectomy. Their mean age was 46.8 years (SD 11.3) and parity was 2.3. Eleven of these had been operated on previously for incontinence.

The pre-operative investigation consisted of a clinical history and examination. Objective assessment comprised independent urine peak flow rate measurement, cystoscopy and video-cystourethrography (VCU), which included provocative tests to exclude detrusor instability. Selection for either operation was made prior to the investigations. The colposuspension was a modification of Burch's (1961) original procedure with more extensive dissection of the bladder base and the final placement of 4 pairs of sutures (Stanton and Cardozo, 1979). The patients were

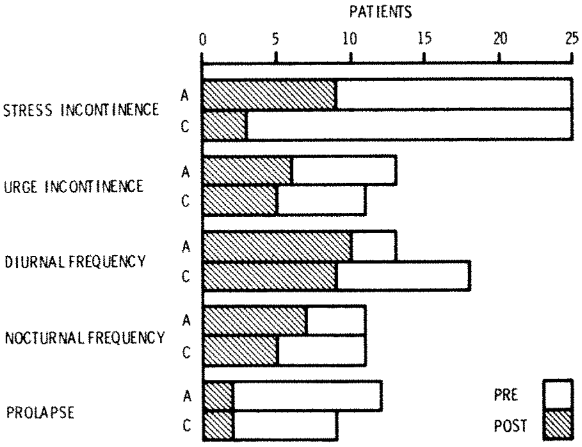

Fig. 1 The pre-operative and post-operative symptoms of patients who had undergone an anterior repair (A) or a colposuspension operation (C).

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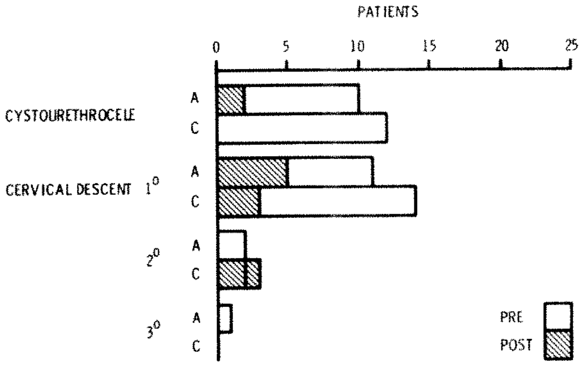

Fig. 2 The pre-operative and post-operative vaginal findings of patients who had undergone an anterior repair (A) or a colposuspension operation (C).

assessed between 3 and 6 months following surgery by clinical methods, videocystourethrography and the Urilos nappy test (Stanton and Ritchie, 1977).

Results

The pre-operative and post-operative symptoms and vaginal signs are shown in Figures 1 and 2 respectively. Pre-operative and post-operative urodynamic data are shown in Tables 1 and 2 respectively.

The objective evidence of cure of stress incontinence is demonstrated in Table 3. Marked incontinence was defined as an obvious loss of contrast on the first cough, whereas slight incontinence occurred on the second or third cough and was less obvious.

Following the anterior repair, 16 patients demonstrated incontinence on VCU, 3 of whom had a positive Urilos test. This resulted in an objective cure rate of only 36% for the anterior repair compared to 84% for the colposuspension procedure.

Table 1 Pre-operative Urodynamic Data

	Anterior repair		*Colposuspension*	
	Mean	*SD*	*Mean*	*SD*
Residual (ml)	46.8	100.0	4.4	20.0
First sensation (ml)	184.3	113.7	185.2	131.5
Capacity (ml)	525.2	105.7	501.2	92.8
PR_1 (cm H_2O)	4.6	3.3	3.7	3.2
PR_2 (cm H_2O)	2.8	4.0	1.7	3.7
Maximum voiding pressure (cm H_2O)	27.7	14.1	27.6	15.7
Peak flow rate (ml/s)	25.4	9.1	27.2	19.0
Descent of bladder neck	13		10	

Table 2 Post-operative Urodynamic Data

	Anterior repair		*Colposuspension*	
	Mean	*SD*	*Mean*	*SD*
Residual (ml)	39.2	60.1	27.6	39.1
First sensation (ml)	251.6	140.6	207.0	88.1
Capacity (ml)	552.0	127.1	489.2	32.3
PR_1 (cm H_2O)	4.4	4.5	7.2	4.3
PR_2 (cm H_2O)	2.0	3.1	3.9	5.3
Maximum voiding pressure (cm H_2O)	33.5	18.9	43.8	12.7
Peak flow rate (ml/s)	21.9	7.6	16.0	10.1
Descent of bladder neck	4		1	

One colposuspension patient developed a cerebrovascular accident following operation but subsequently recovered without any neurological deficit.

Discussion

Objective evidence of stress incontinence after an incontinence-correcting operation is necessary to confirm or refute the patient's history and to demonstrate whether the operation has failed. It usually produces a lower success rate than subjective evidence alone.

The traditional role of the anterior repair for the correction of anterior vaginal wall prolapse can be challenged by the modified colposuspension operation. Although these preliminary results refer only to a 6-month follow-up, additional follow-up of the colposuspension procedure indicates that the correction of anterior vaginal wall prolapse is maintained in over 90% of patients we have seen as a 2-year follow-up.

Stress incontinence due to urethral sphincter incompetence is also conventionally treated by the anterior repair. Cure rates have usually been lower than for suprapubic operations (Bailey, 1954; Jeffcoate, 1967). The disadvantages of these series is the absence of pre-operative and

Table 3 Objective Evidence of Cure of Stress Incontinence

	Anterior repair	*Colposuspension*
VCU		
marked leak	4	0
slight leak	12	1
Urilos positive	3*	3
Objective cure	9 (36%)	21 (84%)

* All incontinent on VCU.

post-operative objective assessment and only one procedure was studied in each report. Our preliminary study suggests that more effective control is achieved by the colposuspension operation, confirming the experience of Hodgkinson (1970) and Morgan (1973) with suprapubic procedures.

It should be noted that the patients who had an anterior repair were 8 years younger than those patients who had a colposuspension. The effect of this on the cure of incontinence may be offset by a previous history of incontinence operations encountered in 11 patients in the colposuspension group and only 3 patients in the anterior repair. It is our intention to continue this study to detect late recurrence of stress incontinence and prolapse and to include more patients so that there will be fewer differences in age and past surgery between the 2 groups.

The mechanism of correction of stress incontinence is dependent upon successful elevation of the bladder neck and proximal urethra to within the abdominal zone of pressure. It would seem that, in addition, there is some outlet narrowing as shown by an increase in maximum voiding pressure and a decrease in peak flow rate in patients following both procedures.

We could find no evidence that the anterior repair predisposed to post-operative symptoms of urgency and frequency, as have been noted by other clinicians. In fact these symptoms appeared to decrease and it is likely that incomplete history-taking prior to anterior repair or an inadequate recall by the patient after the operation are responsible for their apparent increase. We do not feel that either operation should be performed solely to achieve a reduction in urgency and frequency.

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Intravesical Lignocaine and Detrusor Instability

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Summary—The effect of intravesical lignocaine solution on detrusor instability of mixed aetiology was examined in 20 patients; 40 ml of 1% lignocaine solution with 40 ml of 8.4% sodium bicarbonate solution was instilled into the bladder. This produced increased bladder capacity in 19, altered bladder sensation in 9, changed the character of the cystometrogram in 9, and lowered the maximum detrusor pressure during bladder filling in 16. The symptomatic effect of lignocaine was short-lived in all but one patient in whom it lasted 24 h.

The possible mechanism of this inhibitory effect on bladder function is discussed.

Detrusor instability frequently gives rise to the symptoms of frequency, urgency and incontinence and is difficult to manage. In the absence of a treatable underlying cause in the majority of patients the main approach to the problem has been to modify the neuronal influences on bladder behaviour by the use of drugs acting either on the central nervous system or locally on the bladder, by surgical denervation at all levels between the sacral nerve roots and the bladder itself; and by prolonged bladder distension, psychotherapy, bladder training and biofeedback techniques.

Little attention has been given to the use of selective neurotoxic agents applied locally to the bladder, and in particular to local anaesthetic compounds, which at other sites have potent but reversible nerve blocking action. George (1978), however, showed that 8 of 26 patients with detrusor instability became stable following the instillation of 8 ml of 2% lignocaine into the bladder.

In this paper we report the effect of intravesical lignocaine on bladder function in 20 patients with proven detrusor instability.

Patients and Methods

Twenty patients were studied: 16 were female (mean age 50 years with a range of 25 to 71 years) and 4 were male (mean age 28 years with a range of 18 to 37 years). In 17 the detrusor instability was idiopathic and in 2 it was neurogenic (post-meningitis and a lipoma of the spinal cord).

In all patients detrusor instability was initially diagnosed during a standard urodynamic assessment which included a cystometrogram, urethral pressure profile measurement, and cineurethrocystography with synchronous recording of urine flow rate and volume, rectal and bladder pressures. Urine culture, intravenous urography, cystoscopy and full neurological examination were performed to exclude any treatable underlying cause for the instability.

The patients returned later for the purpose of this investigation.

The local anaesthetic used in the study was lignocaine hydrochloride B.P. 1% w/v.

Three supine cystometrograms were performed before instillation of the lignocaine solution. Bladder pressure was measured through a 3 FG urethral catheter and the bladder filled at a rate of 100 ml/min through a separate 12 FG urethral catheter. The rectal pressure was measured through a fluid-filled catheter in the rectum. Detrusor instability was defined as a rise in detrusor pressure of 15 cm of water or more at any time during bladder filling.

The patients' subjective response to bladder filling was carefully recorded and in particular the bladder volume at the time of the first sensation of the desire to void was recorded. The patients were asked for a subjective impression of the severity of urgency during and at the end of filling. Filling was continued until either the patient leaked or had an unbearable desire to void. This end point was defined as the bladder capacity. The maximum detrusor pressure developed during filling was measured.

The bladder was then emptied and 40 ml of 1% lignocaine solution introduced with 40 ml of

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an 8.4% solution of sodium bicarbonate. The latter rendered the bladder contents alkaline. After 15 min the patient was moved from a supine to semirecumbent position for a further 15 min, following which 3 further cystometrograms were performed and the same observations made.

Following these cystometrograms the bladder was filled to capacity with saline and the patient asked to void, when simultaneous recordings of bladder and rectal pressures, urine flow rate and volume were made.

The type of cystometrogram obtained in each patient was categorised into one of 3 types, and any change in this general pattern following lignocaine noted:

1. A "systolic" type in which the detrusor pressure rose abruptly from the baseline which altered little.
2. A "steady pressure rise" type in which the baseline rose steadily during filling.
3. An "undulating systolic" type which had the features of both (1) and (2). The baseline pressure rose steadily during bladder filling but there were also intermittent systolic contractions.

The following variables were measured in all patients before and after intravesical lignocaine:

(*a*) The bladder capacity.
(*b*) Bladder sensation during filling.
(*c*) The volume at which the first desire to void occurred.
(*d*) The character and type of the cystometrogram.
(*e*) The maximum detrusor pressure developed during filling.
(*f*) Voiding urodynamics.

Statistical analysis of the results was by the appropriate Student's t-test.

Results

All 20 patients tolerated the investigation well; none were excluded. There were no local or systemic adverse reactions to the local anaesthetic solution.

Bladder Capacity

The mean and range of the 3 bladder capacities in each patient measured before and after intravesical lignocaine are shown in Figure 1. There was considerable overlap in the range of capacity but in 19 patients the increase in capacity varied from 14 to 900% and was statistically significant ($P<0.001$). The bladder capacity decreased in only one patient. The sequential capacities measured before lignocaine instillation showed little variation, whereas the capacities measured

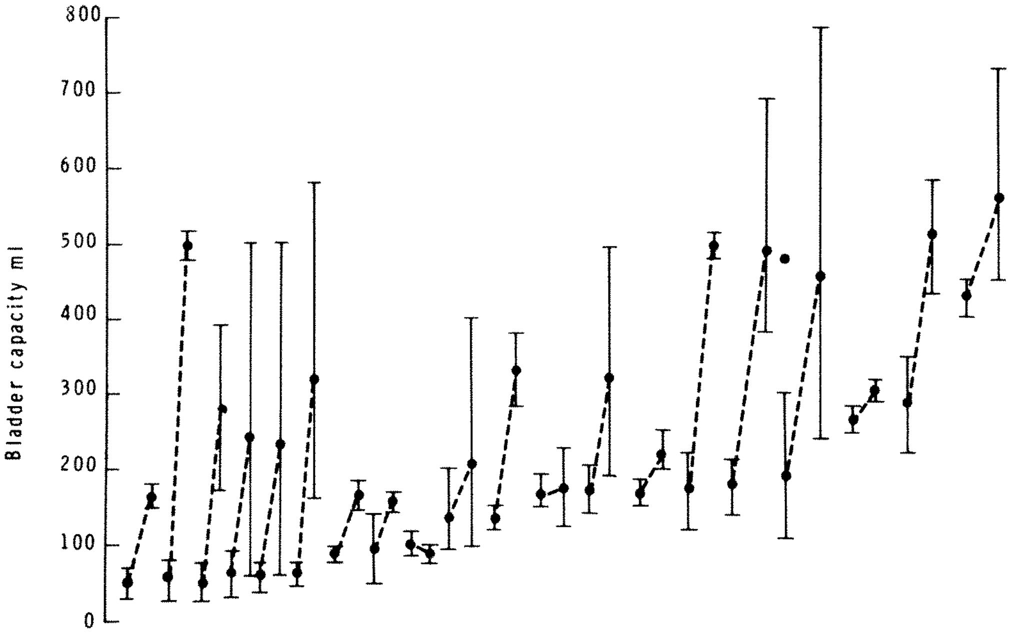

Fig. 1 The change in the mean and range of bladder capacity in each patient following 400 mg intravesical lignocaine.

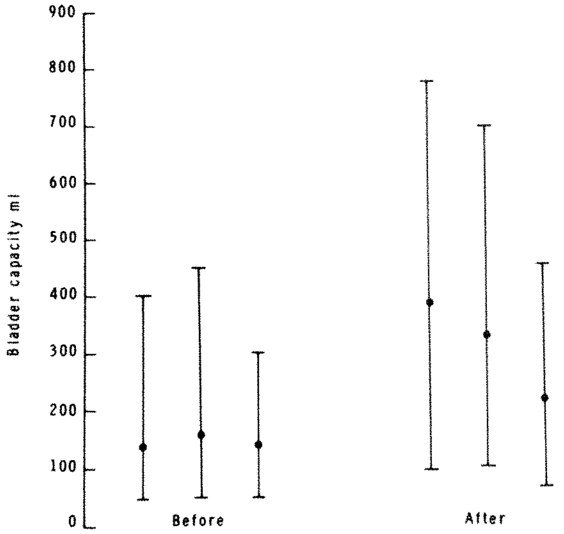

Fig. 2 The mean and range of bladder capacity for the whole series of patients during 3 cystometrograms before and after 400 mg intravesical lignocaine.

after showed a steady decrease (Fig. 2). The mean bladder capacity of the whole series of patients increased from 146 ml (range 50-400 ml) to 326 ml (range 60-780 ml) after lignocaine ($P<0.001$).

Bladder Sensation

This was altered in 9 patients following lignocaine. Eight noticed that the intensity of their urgency was less, and in one patient bladder sensation was abolished completely. In 2 patients the desire to void became a suprapubic ache.

First Sensation Volume

The mean bladder volume at which the first desire to void occurred increased from 162 ml (range 85-300 ml) before, to 314 (range 130-730 ml) after lignocaine instillation ($P<0.02$). (This was accurately recorded in only 12 of the 20 patients.)

Cystometrogram Changes

Before lignocaine instillation 18 patients had a "systolic", and 2 had an "undulating systolic" type of cystometrogram. Following lignocaine a change in the type of character of the cystometrogram was seen in 9 patients, but all remained unstable according to the definition given earlier. The changes which occurred are summarised in the Table. Five of the 9 patients whose cystometrograms changed noticed alteration in their symptoms during bladder filling.

Table The Change in the Type of Cystometrogram After 400 mg Intravesical Lignocaine*

Before	*After*
Systolic 18	Unchanged 10
	Undulating systolic 5
	Steady pressure rise 3
Undulating systolic 2	Unchanged 1
	Steady pressure rise 1

* See text for definition of types of cystometrograms.

Maximum Detrusor Pressure During Filling

The maximum detrusor pressure which developed at any time during filling was lower in 16 of the 20 patients following instillation of lignocaine. The mean value of this pressure for the whole series of patients decreased from 65.5 cm H_2O (range 35-100 cm) to 44.5 cm H_2O (range 20-100 cm) ($P<0.001$).

Voiding Urodynamics

There was no change in the rate of voiding or detrusor pressure during voiding following lignocaine instillation.

Discussion

Lignocaine was the local anaesthetic chosen for this study as it is known to produce effective mucosal anaesthesia when applied as a concentrated gel to the urethra and to other mucous membrane surfaces, *e.g.* the tracheobronchial tree. It has been shown to have little systemic toxic effect when applied in high doses to the rabbit bladder, and at this site has a very high LD_{50} (Astrom and Persson, 1961).

Initial pilot studies of the effect of intravesical lignocaine were disappointing until we realised that the pH of the bladder cavity might be important to achieve optimal effect from the local anaesthetic solution. Ritchie *et al.* (1965) demonstrated that the active form of local anaesthetic compounds of the lignocaine type is the positively charged cation which, in solution, is in equilibrium with the uncharged base form. The latter, however, diffuses more rapidly through tissues. At an alkaline pH the dissociation favours the uncharged base form and hence if the bladder contents are alkalinised more lignocaine is in a form which will readily diffuse through the mucosa.

The results suggest that lignocaine solution at a dose of 400 mg does alter bladder function. The mechanism of this action is, however, not clear. The modalities of bladder function which are changed, *i.e.* bladder capacity, sensation, the character of the cystometrogram and the amplitude of detrusor contractions during bladder filling, are all mediated via complex nervous pathways involving bladder sensory receptors, centres in the brain and spinal cord, peripheral nervous connections and the detrusor muscle itself.

The effect of lignocaine on both bladder capacity and the maximum detrusor pressure developed during filling could reflect either motor or sensory nerve inhibition or depression of the detrusor muscle directly, but the effect on bladder sensation is almost certainly due to inhibition of sensory nerves or sensory receptors. Histological evidence for both sensory nerves and receptors within the mammalian bladder is scant, but the fact that they may be blocked by intracavity local anaesthetic solution would suggest that they may be in the submucosal region as tissue penetration by lignocaine is poor. The type of receptor upon which bladder sensation depends is also not known but they may be stretch receptors or receptors which respond to a deforming force whose threshold for depolarisation is raised by local anaesthesia. The intensity of urgency may depend on the number of receptors firing at any one time, and local anaesthetics may reduce this number.

The change in the character of the cystometrogram may also reflect either nerve or direct detrusor inhibition. The conversion of a "systolic" type of cystometrogram in 5 patients to an "undulating systolic" type with a rising baseline suggests that the neuromuscular basis for the different types may be different. It is possible that the steadily rising baseline may reflect detrusor hypertrophy or a response of the detrusor muscle *itself* to filling.

There appears to be little correlation between any change in the type of cystometrogram and alteration in bladder sensation, for only 5 of the 9 patients whose cystometrogram changed had any alteration in bladder sensation, and 4 patients whose cystometrogram remained unchanged noted change in their symptoms.

Local anaesthetic agents have many other actions including ganglion blockade, anticholinergic and antihistaminic activity, all of which may affect bladder function. It is not possible on the basis of the present study to implicate any of these components of local anaesthetic action in the change in bladder function.

The symptomatic effect of lignocaine was short-lived in all but one patient. This finding is not unexpected as lignocaine has a short duration of action when used for infiltration and topical anaesthesia at other sites. The rapid decline in effect in successive cystometrograms is, however, more difficult to explain. It is possible that the dose of anaesthetic used in this study was too low, for it is recognised that the duration of action of local anaesthetics is partly dependent on the dose used (Covino and Vassallo, 1976).

The effect of sodium bicarbonate alone on bladder function was examined in 5 patients, and no change was detected.

We conclude that 400 mg of lignocaine solution, instilled into the urinary bladder in the presence of detrusor instability, may produce a significant alteration in bladder function with a reduction in bladder overactivity, but does not, at this dose, abolish instability. It is important that the bladder contents be alkalinised for the most effective action of the lignocaine solution. The mechanism of bladder inhibition during filling is uncertain, but may reflect both nervous and smooth muscle inhibition.

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A Double-blind Crossover Trial of Baclofen—a New Treatment for the Unstable Bladder Syndrome

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Summary—Forty patients with the unstable bladder syndrome have been treated in a double-blind crossover trial of baclofen 5 mg qds versus placebo. Baclofen significantly improved diurnal and nocturnal frequency of micturition and the severity of incontinence. Considerable improvement was also obtained with placebo.

Baclofen (Lioresal-CIBA) is a derivative of gamma-amino butyric acid, which is an inhibitor of spinal synaptic transmission, being particularly active in depressing reflexes. It is a new drug in the treatment of the unstable bladder syndrome, though it has been used in patients who have neurogenic bladders following spinal injuries or in medical conditions such as multiple sclerosis and syringomyelia.

Roussan and Gordon (1973) were amongst the first to investigate its urological effects. In 3 cases, 2 of multiple sclerosis and one of transverse myelitis, they found that it not only reduced voluntary sphincter activity but also involuntary detrusor activity. The latter finding has not really been followed up. Hachen and Krucker (1977) confirmed the sphincter relaxation but could not show an effect on the detrusor muscle; however, these patients were suffering from traumatic paraplegia.

Materials and Methods

The dose of baclofen used was low at 5 mg qds (doses of up to 100 mg per day have been used for the relief of muscular spasm).

Side effects have been few and are outlined in Table 1. Only 3 patients had to stop treatment and one of these was taking the placebo at the time. The female patient who suffered from sexual insatiability was certain that this was due to the drug, as it stopped immediately on cessation of therapy and recurred when the drug treatment was resumed. This has not been previously recorded.

Table 1 Side Effects

Sedation	3	All active drug. All mild.
Nausea	2	1 active drug. Stopped treatment 1 placebo—mild.
Dizziness	1	Placebo. Stopped treatment.
Sexual insatiability	1	Active drug. Stopped treatment.

Forty patients were entered into a double-blind crossover trial using matched placebo; 20 were put into each group; thus half started on the active drug and half on placebo. After 28 days they were crossed over to the other preparation which they took for a further 28 days. The sex ratio was 2:1, females to males.

Before starting treatment they filled in a questionnaire to establish the pre-treatment levels of the following: frequency of micturition by day, frequency of micturition by night, episodes of incontinence, number of pads required per day, and frequency of enuresis. They were given score sheets to take home so that they could keep a note of their performance under these headings. A space was provided for patient comments and they were also questioned at the end of the treatment period as to the timing of relief of symptoms.

Results

The results of the individual observations are shown

Table 2 Symptomatic Results

	Baclofen	*Placebo*
Improved	21 (52.5%)	16 (40%)
No change	15 (37.5%)	22 (55%)
Worse	4 (10%)	2 (5%)

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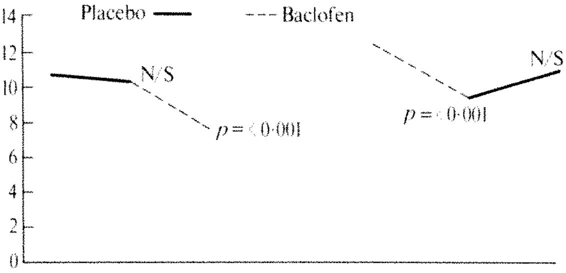

Fig. 1 Frequency: Number of micturitions by day.

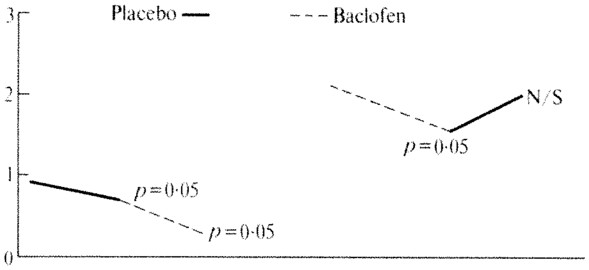

Fig. 3 Number of pads used per day.

in Figures 1 to 3. The sex ratio did not differ in the various groups.

Figure 1 shows that after starting treatment with the placebo there was no significant effect on diurnal frequency; however, baclofen significantly improved the performance in the second month. Starting with baclofen there was a significant initial improvement; this was maintained in the second month with no change.

The effect on nocturnal frequency is shown in Figure 2. There was a significant reduction by placebo with a further significant fall while on baclofen in the second month. When placebo followed the active drug, there was a statistically significant deterioration in the second month.

The pattern for frequency of incontinence was exactly the same as for nocturnal frequency. This was reflected in the resulting reduction in the number of pads used, as shown in Figure 3, though the numbers were smaller. There was no significant effect on enuresis.

The results achieved a high level of statistical significance in most cases, but we were also interested in the subjective response. Table 2 shows the results taken from the patients' own comments. There was a close correlation between the patients' subjective reduction in symptoms and the taking of baclofen. Many of the patients described a marked reduction in the sensation of urgency and this included several who had no objective reduction in urinary frequency.

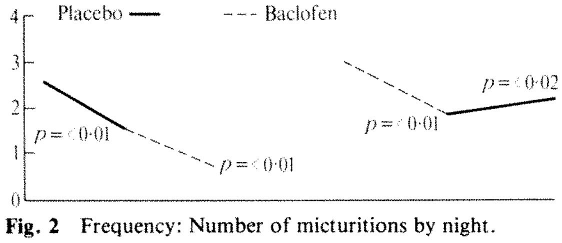

Fig. 2 Frequency: Number of micturitions by night.

Thirteen patients have been followed up for a period of 6 months. Nine had maintained their improvement and 4 had relapsed. Those who relapsed were retreated with baclofen at the same dose of 5 mg qds. Two responded for a second time and 2 did not.

It is concluded that baclofen is a useful drug in the unstable bladder syndrome. Its mode of action is unclear but it is an alternative to the standard anticholinergic therapy. At a dose of 5 mg qds the side effects have not been a problem. The long-term results are encouraging.

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Hesitancy and Poor Stream in Younger Men without Outflow Tract Obstruction—the Anxious Bladder

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Summary—Sixteen younger men who presented with frequency, hesitancy and poor stream have been examined by clinical, urodynamic and endoscopic means. These urological symptoms have been found to be associated locally with a poor detrusor action and generally with a high incidence of dyspepsia and anxiety disorder. It is suggested that an initiating factor may be common to all 3 systems and hence a general rather than a local solution should be sought.

Hesitancy and poor stream in men under 55 years of age are commonly associated, in the absence of neurological impairment, with degrees of obstruction in the outflow tract either due to bladder neck hypertrophy or early adenomatous enlargement of the prostate gland. In these cases clinical, endoscopic and urodynamic findings are usually in agreement as to the site and nature of the obstructive problem.

A series of patients is described in which the symptoms of frequency, hesitancy and poor stream are associated with a particular urodynamic pattern and absence of convincing endoscopic abnormality. In addition, these patients commonly complain of gastrointestinal dyspeptic symptomatology and psychological problems, often severe enough to disrupt their daily lives.

Patients and Methods

All patients were referred by Avon Area Consultant Urologists for urodynamic studies because of persistent lower tract symptoms not responding to conventional methods of treatment: 84 male patients were studied between the ages of 20 and 55 years and 16 patients were found to conform to the syndrome described above (age range 29 to 55 years, mean 42 years).

Patients were interviewed prior to urodynamic tests by one investigator (N.G.) who subsequently performed the studies. Answers to detailed questions concerning urological, gastrointestinal, neurological and cardiovascular systems were recorded on a computerised proforma.

Urodynamic studies were performed as an outpatient procedure by the investigator and one assistant alone with the subject in a quiet warm room devoid of other persons or equipment which might distract the patient. Prior to the studies the patient filled in a 14-day frequency/volume chart whilst in his normal home/work environment. Accurate and objective data on the frequency and physiological volumes voided were thus available prior to the test. During all voiding procedures patients were entirely alone in the room, passing urine into a commode of normal appearances.

Intravesical pressures were recorded from a 16-

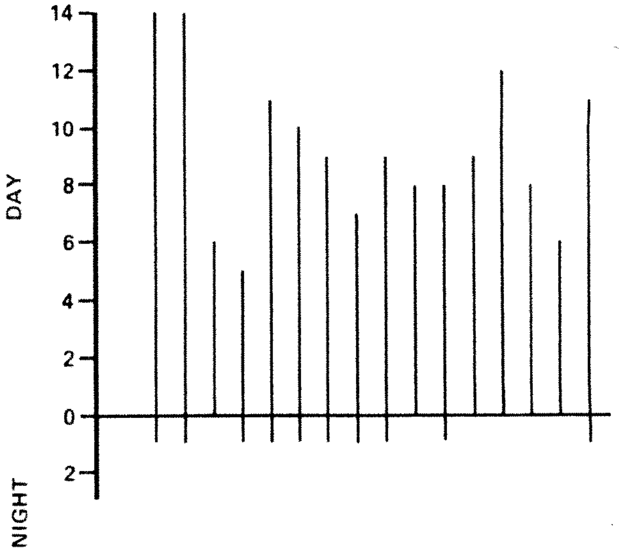

Fig. 1 Frequency—day/night.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

gauge epidural catheter *per urethram*, this being the only catheter present in the urethra during voiding studies. A rectal balloon pressure catheter enabled subtracted detrusor pressure to be recorded on an Elema M81 ink jet recorder via Elema EMT 34 pressure transducers. Synchronous flow studies were obtained from an EMT 435 uroflowmeter.

Endoscopic findings were recorded by the consultant in charge of the case with the urodynamic investigator present where possible.

Results

The typical clinical picture in these 16 patients conforming to the syndrome will be described, followed by the urodynamic and endoscopic findings.

Urological Symptom Complex

Daytime frequency was marked, whereas nocturia was conspicuously absent by comparison (Fig. 1). Patients complained of persistent sensory urethral desire to void which did not require voluntary sphincter activity as a counter measure. Invariably frequency was least noted when concentrating on a task (*i.e.* at work), whilst more troublesome when relaxing at home. Hesitancy was severe in 15 out of 16 patients. Most attempted to push to keep their stream going, which was otherwise poor and intermittent in nature.

Of especial interest was the inability of the majority to micturate when in a public urinal—patients either chose a closet or preferably returned home to void in the peace of their own surroundings. Other common symptoms were suprapubic bladder pain, worse if micturition was delayed, loin to groin ache and dysuric voiding pains in the absence of urinary infection. Incontinence was not a feature but the majority complained of a post-micturition dribble which turned out to be of minor degree and was probably related to their fastidious nature (see below).

Gastrointestinal Symptom Complex

Foregut dyspepsia was common to these patients: 10/16 had regularly prescribed antacids from their general practitioners and 5/16 had had previous oral barium studies. Hind gut symptoms were uncommon by comparison—only 3 patients describing spastic colon-like symptomatology.

Psychological Symptom Complex

Most patients were self confessed "worriers" and appeared excessively anxious at interview. Obsessive neuroses chiefly concerned with their work and personal health were common and 2 patients had marked cancerophobia.

On direct questioning sexual problems of various types were evident and in some patients these seemed to be the basis of their anxiety. At some time tranquillisers had been tried in the majority of patients.

On examination all patients appeared fit and in no patient were signs detected in the peripheral nervous system. Haemoglobin and urea/electrolyte estimations were normal in all patients.

Urodynamic Findings

Flow rate was poor (range 5-15 ml/s, mean 11 ml/s) and typically intermittent in nature (Fig. 2). This poor flow was found to be due in all cases to detrusor contractions which were weak and poorly maintained (Fig. 3). In no case did the subracted detrusor pressure approach a level which could be diagnosed as obstructive in nature.

Physiological bladder capacity was reduced in 15 out of 16 patients (Fig. 4). The mean capacity at the normal desire to micturate was 210 ml.

Endoscopic Findings

In no patient was there convincing evidence of outflow tract obstruction. "Mild bladder neck lip", felt minimally *per rectum* against the cystoscope, was the most commonly recorded sign. Most patients had several cystoscopies confirming this finding due to the discrepancy between symptoms

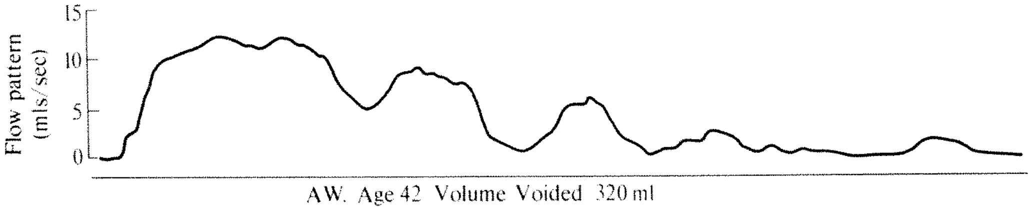

Fig. 2 Flow rate.

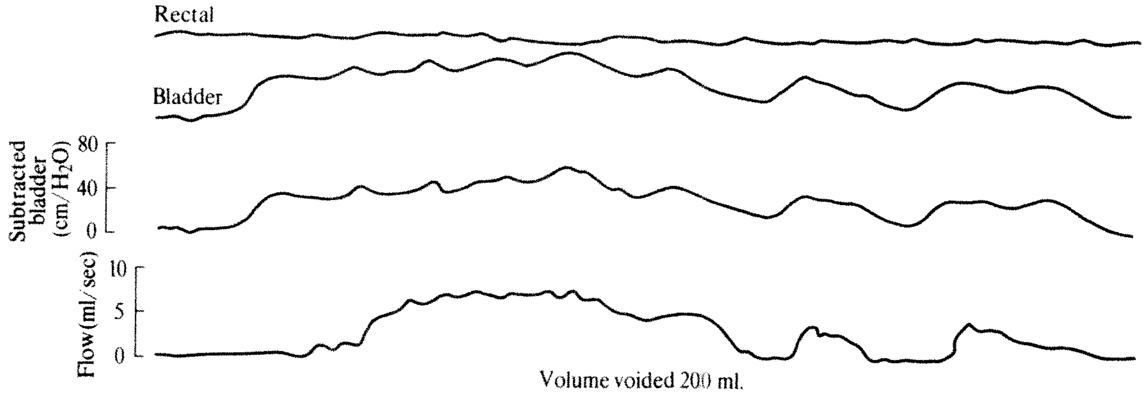

Fig. 3 Urodynamic measurements showing weak and poorly maintained detrusor contractions.

and signs. In view of the young average age of this group resections were unusual; however, 6 resections were carried out in 3 patients but in none of these was any significant improvement noted. The maximum weight resected at these operations was 4 g.

At present the majority of patients remain on regular follow-up and the average duration of symptoms to date is 9 years. Most patients have been discharged once, some several times but all seem inevitably to return with similar symptomatology.

Discussion

In attempting to define a disorder in which symptoms of anxiety appear to play a prominent role it is obviously necessary that meticulous care be taken over the investigation techniques, particularly when these involve invasive studies. In this series every effort was made to interview and investigate under pleasant and "human" conditions. Whenever appropriate (*i.e.* voiding) the patient was left entirely alone in a peaceful, quiet room.

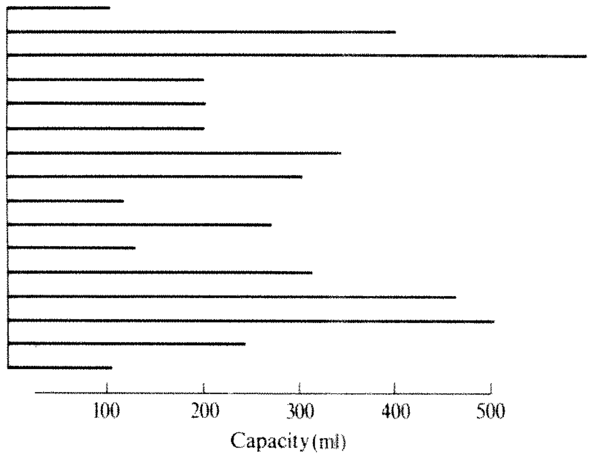

Fig. 4 Bladder capacity.

It would appear from our figures that this condition is common (16 out of 84 patients under 55 years). However, this figure probably illustrates the persistent nature of the problem as seen by the urologist in the out-patient clinic. Although accurate figures are not available, true bladder neck obstruction is likely to be a much more common entity, since these cases are not usually referred for urodynamics as the combination of poor stream and an endoscopically florid bladder neck convinces the clinician as to the nature of the problem.

Of the other 68 patients under 55 years who did not conform to the syndrome, the majority had either true bladder neck obstruction, persistent enuresis or spinal trauma. The incidence of psychological and gastrointestinal symptoms was less in the remainder. Dyspepsia requiring regular antacid therapy was present in 12 of 68 patients.

The incidence of dyspepsia in the general population is difficult to estimate since studies are generally performed in areas which have a high incidence of dyspeptic problems. In 2 such areas Doll and Jones (1951) and Weir and Backett (1968) estimated the incidence of all dyspepsia as 31.0% and 35.2% respectively. The incidence of dyspepsia in the group under study would thus appear to be over twice the estimated incidence in these known ulcer areas.

Psychological symptoms are difficult to quantify objectively. However it is of interest that on reviewing the psychological literature phobic disorders are described in which men have both marked daytime frequency and an unexplained inability to pass urine until the urinal room is empty.

It is because of this sensitivity that the attention to investigative technique already mentioned is important. Initially, video studies were attempted on this group in an attempt to visualise the changes at the bladder neck during voiding, but not surprisingly the patients found it impossible to void any urine under these conditions. Only after removal of X-ray machinery and personnel could the patients expel their urine.

The overall importance of investigation technique has already been stressed; in particular it is important that the patient does not attempt to improve his flow rate by pushing to impress the doctor—a specific warning to pass naturally is required.

Flow rates in this group were poor and hesitancy marked. In every case this was associated with a weak and poorly maintained intrinsic detrusor pressure rise. In otherwise fit young men in this age range such flow rates are usually associated with demonstrable endoscopic abnormalities. Urodynamically the intrinsic detrusor pressure associated with these flow rates would be expected to be high, often exceptionally so. Pressures of 150 to 200 cm of water are frequently recorded in such young patients with true bladder neck obstruction. By contrast, in the group described pressures were universally *low*, no patient exceeding 65 cm of water at peak flow. It is this association between low intrinsic detrusor pressure and low flow rate that is so striking in this group.

Low detrusor pressures may be due to other causes. In this group no patient had any clinical sign suggestive of neurological impairment in either somatic or autonomic nervous systems. Some cases of chronic retention may exhibit such low pressure voiding waves with associated low flow and residual urine. The explanation of this is usually that overstretching and/or decompensation of detrusor fibres has occurred whilst the obstructive forces were present. However, in the group under study bladder capacities were found to be on the small side and residual urines were not seen (Fig. 4). It would seem unlikely that overstretching can be the explanation of the poor pressure waves.

It should thus be emphasised that the diagnosis of "anxious bladder" cannot be made without urodynamic data even though it may be suspected from the history, clinical examination and negative endoscopic findings. Young men with conventional bladder neck obstruction may easily be worried about their stream; pressure studies are essential to determine whether the low flow is associated with high or low pressure detrusor waves.

We propose the existence of a chronic systemic state which may manifest itself in various guises; in the central nervous system by anxiety and phobic disorder, in the gastrointestinal system by a dyspeptic diathesis, and in the urological system by frequency, hesitancy and poor flow associated with a poor detrusor contraction. It is possible to support this hypothesis with pharmacological evidence—the fundus of the bladder is known to be innervated by beta-adrenergic relaxor fibres. Thus a sympathetically mediated systemic anxiety state might conceivably produce the effect noted. As yet, however, no objective proof of inhibition of detrusor activity by adrenergic neurones, whether at local or ganglionic level, has been produced.

Logically we conclude that local therapy to the lower urinary tract is unlikely to be of value in this condition—and the results of surgery in this series appear to bear this out. It seems likely that a different systemic solution to the problem will be required.

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Selective Sacral Neurectomy in the Management of Urinary Incontinence due to Detrusor Instability

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Summary—Since Torrens (1974) reported on the use of selective sacral neurectomy in the management of bladder instability, the procedure has been used increasingly in specialised centres.

We report the clinical and urodynamic findings in 9 patients in whom this procedure has been performed. The results suggest that selective sacral neurectomy is a valuable procedure in a highly selected group of patients with neurogenic bladder dysfunction. Patient selection, contraindications and the choice of which sacral nerves to divide are discussed.

Detrusor instability is a common finding in incontinent patients; it may be associated with neurological disease or it may occur in its absence. Most patients with bladder instability will respond to anticholinergic medications (Vinson and Diokno, 1976) and a wide variety of other treatments has been used, *e.g.* overdistension of the bladder, instillation of astringent solutions and psychotherapy. There is, however, a small group with severe incontinence which fails to respond to these treatments. In some patients the detrusor instability is so severe that management of incontinence with an indwelling urethral catheter fails because of expulsion of the catheter or leaking around it.

Another mode of treatment of detrusor instability is denervation of the detrusor. Torrens (1974) demonstrated that blocking either the S2, 3 or 4 nerve roots bilaterally produced a marked increase in bladder capacity and decrease in uninhibited detrusor contractions with little change in urethral sphincter activity. These findings were most pronounced with the S3 nerves. On the basis of these studies he advocated selective sacral neurectomy for the management of the unstable bladder.

We present the results of selective sacral neurectomies performed in 9 patients over a period of 3 years.

Patients and Methods

The patients were selected from over 2000 referred to the Urodynamic Clinic on the basis of the severity of their symptoms and the failure of drug therapy and other forms of treatment (Table 1). In 4 patients a diagnosis of disseminated sclerosis had been made: in 2 patients from this group the indication for operation was inability to retain a Foley catheter. A traumatic-paraplegic female was included for the same reason. In 4 patients the primary complaint was enuresis, but all had diurnal symptoms in varying degrees: in 2 of these patients there was no other demonstrable neurological anomaly; one had had a cervical meningomyelocoele closed at birth, without residual neurological defect, and the fourth had grand mal epilepsy and spina bifida occulta.

Urodynamic Assessment

All patients had urodynamic assessment at least once before and after the procedure, with pressure flow studies and synchronous fluoroscopy as previously described (Thomas *et al.*, 1975). Bladder filling was at the rate of between 10 and 50 ml/min depending on the severity of the patient's symptoms. Wherever possible studies were performed in the upright position.

Operative Techniques

With the patient in the prone position under light general anaesthesia a midline incision was made to expose the sacrum. The sacral hiatus was then exposed and a laminectomy was performed cephalad to expose the sacral nerves extradurally. The nerves were then stimulated using a voltage of 20 volts with 100 Hz repetition rate and 0.5 ms

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Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 1

Patient	*Sex*	*Age*	*Complaint*	*Diagnosis*	*Result*
J.R.	M	21	Enuresis	Spina bifida occulta, grand mal epilepsy	Good
D.S.	F	29	Diurnal incontinence	Disseminated sclerosis	Very good
D.G.	F	43	Unable to retain I.D.C.	Disseminated sclerosis	Good
A.W.	M	17	Enuresis	Cervical meningomyelocoele	Failure
G.L.	M	31	Enuresis	Idiopathic	Failure
C.M.	F	24	Enuresis	Idiopathic	Good
N.S.	F	38	Diurnal incontinence	Disseminated sclerosis	Good
J.M.	F	56	Unable to retain I.D.C.	Disseminated sclerosis	Good
A.C.	F	9	Unable to retain I.D.C.	Traumatic paraplegia	Good

pulses, giving 100 ms bursts every 1.5 s. The intravesical pressure was monitored via a urethral catheter and the response to stimulation of the various sacral nerves recorded as a guide to which nerves to section. The chosen nerves were then sectioned and a length resected. Post-operatively an indwelling urethral catheter was left for 3 or 4 days.

Results

Good results were reported by 7 of the 9 patients (Tables 1 and 2). All 3 patients who were unable to retain an indwelling catheter pre-operatively, even when taking anticholinergic drugs, could do so post-operatively and did not leak around it, although 2 patients continued taking anticholinergics. The third patient (D.G.) was able to remain catheter-free for 2 years post-operatively taking medication, but progressive disseminated sclerosis then necessitated a return to a catheter.

The 2 patients with disseminated sclerosis who had been severely incontinent pre-operatively (D.S. and N.S.) both reported almost complete disappearance of their symptoms in the early post-operative phase, after section of S3 nerves bilaterally and on 2-year follow-up they were still greatly improved, although one (N.S.) was taking

Table 2

Patient	*Pre-operative symptoms*	*Details of operation*	*Result*
J.R.	Life-long enuresis, frequency	Right S3 divided Left S3 crushed	Initially had excellent result, 2½ years later was taking anticholinergics, had occasional urgency, very rare enuresis
D.S.	Urge incontinence, frequency, enuresis, spastic paraparesis	Left S3 divided Right S3 crushed	Good response for 4 months, but after 9 months symptoms were not controlled by drugs
		Right S3 divided 10 months later	No incontinence, frequency or urgency, mild nocturia
D.G.	Paraparesis, unable to retain indwelling catheter (I.D.C.)	Bilateral S3 division	Completely continent for 12 months, but by 24 months needed catheter to stay dry
A.W.	Life-long enuresis and diurnal incontinence, severe urgency	Bilateral S3 division Left S2 division	Initially voided by straining then developed overflow incontinence and upper tract dilatation. Had urinary diversion 5 months later
G.L.	Enuresis, mild urgency and frequency	Bilateral S3 division	Enuresis returned after 3 months, has not responded to medication
C.M.	Life-long enuresis, urgency and urge incontinence	Bilateral S3 division	Initially greatly improved, by 20 months was taking imipramine, had enuresis (approx. twice weekly) moderate urgency but no daytime incontinence
N.S.	Enuresis, nocturia (× 3-4) Frequency, urgency and urge incontinence	Bilateral S3 division	No nocturia or enuresis at 18 months taking anticholinergics had mild frequency and occasional urge leakage
J.M.	Paraparesis, unable to retain I.D.C.	Bilateral S3 division	Retains I.D.C. without leakage, taking oxybutynin (12 months)
A.C.	Reflex neurogenic bladder, unable to retain I.D.C.	Bilateral S4 division Left S3 division	Retains I.D.C. no leakage, taking imipramine (9 months)

anticholinergic medication at that time. One of these patients (D.S.) had only her left S3 nerve sectioned at the time of her original operation. She had a good response for 4 months, but then her symptoms began to return and urodynamic evaluation showed marked uninhibited detrusor contractions. At a second procedure the right S3 nerve was sectioned and since then the patient has been very well.

Of the 4 patients whose primary diagnosis was enuresis, 2 (J.R. and C.M.) have had good results and their symptoms are now controlled with anticholinergic medication. One of the male patients (A.W.), whose pressure flow studies pre-operatively showed gross instability and marked detrusor-sphincter dyssynergia, was improved initially but later complained of dribbling incontinence. An intravenous urogram revealed marked deterioration of the upper urinary tract and repeat urodynamic studies showed a hypertonic filling phase. He required a supravesical diversion 5 months after his sacral neurectomy.

The last patient (G.L.) had suffered from enuresis all his life, with only mild urgency and frequency by day. His pre-operative pressure studies showed no abnormality until a capacity of 450 ml was reached, when there was an unstable contraction and complete incontinent voiding. After bilateral S3 nerve division he had a good result initially but complained of severe buttock pain. His enuresis returned after 3 months, however, and has persisted in spite of other measures. Post-operative urodynamic assessment showed no abnormality.

Post-operative urodynamic assessment revealed persistence of some instability in the majority of patients (Table 3). Although most patients voided by straining, some were able voluntarily to initiate a detrusor contraction. One patient (A.W.) had a significant amount of residual urine. There was no evidence on any of the post-operative urodynamic assessments of urethral sphincter weakness or of vesicoureteric reflux. No patient reported any change in bowel pattern. None of the male patients had any change in their patterns of erection or ejaculation. The only significant morbidity was buttock pain in one patient. Average follow-up is now 2 years.

Discussion

Although sacral rhizotomy has been a suggested mode of management for the reflex neurogenic bladder associated with spinal cord injury for many years (Meirowski *et al.*, 1950) the use of the technique in paraplegics has never gained wide acceptance. Following the demonstration by Torrens (1974) of the possibility of selectively denervating the detrusor without altering urethral

Table 3

Patient	*Pre-operative urodynamics*	*Post-operative urodynamics*
J.R.	Gross instability (to 150 cm H_2O) at 120 ml cap. Incontinent	Uninhibited contractions to 50 cm H_2O at 300 ml cap. with incontinence. Unable to initiate detrusor contraction
D.S.	Very unstable (to 160 cm H_2O) at 50 ml incontinent	Unstable contractions to 30 cm H_2O at 150 ml capacity, incontinent *After 2nd procedure* Unstable contractions to 20 cm H_2O cap. 250, not incontinent. Voids by straining
D.G.	Large R.U., instability (to 40 cm H_2O). Incontinent at 400 ml cap.	Stable 2 months later, after 2 years had instability (to 10 cm H_2O) and incontinence
A.W.	Gross instability, large R.U. marked detrusor-sphincter dyssynergia, voided by straining. Cap. 250 ml	Hypertonic filling phase. Cap. 400 ml. Large R.U.
G.L.	Stable to 450 ml then unstable contraction (50 cm H_2O) with incontinence	No instability, large capacity (700 ml) voluntary voiding with good detrusor contraction
C.M.	Unstable contraction (to 60 cm H_2O) at 250 ml capacity with complete involuntary voiding	Unstable contraction (to 15 cm H_2O) at 350 ml. Incontinent at 500 ml
N.S.	Unstable contraction (to 40 cm H_2O) at 120 ml capacity with complete involuntary voiding	Unstable (15 cm H_2O) at 400 ml capacity. Not incontinent, voided by straining. No residual urine
J.M.	Gross instability (60 cm H_2O) at 50 ml capacity. Incontinent	Unstable (15 cm H_2O) at 150 ml cap. Incontinent
A.C.	Unstable (to 70 cm H_2O) capacity 200 ml marked detrusor-sphincter dyssynergia	Stable to 250 ml capacity then hypertonic filling phase (40 cm H_2O at 350 ml capacity)

function, selective sacral neurectomy was utilised in a group of patients who had unstable bladders, producing satisfactory results (Torrens and Griffiths, 1974). Rockswold *et al.* (1978) reported the use of selective sacral rhizotomy in the management of the uninhibited bladder in multiple sclerosis and again demonstrated the possibility of improving continence in ambulatory patients by denervation procedures. Diokno *et al.* (1977) have also reported good results following selective sacral rhizotomy in 7 patients who had uninhibited neurogenic bladders.

Operative Details

The choice of which sacral nerves were to be divided was based largely on the results of intra-operative nerve stimulation. Other series have used sacral nerve blocks pre-operatively but it was concluded by Torrens and Griffiths (1976), after a comparison of the 2 techniques, that intra-operative stimulation was more reliable.

In our first 8 cases stimulation of the S3 nerves bilaterally produced the largest rise in intravesical pressure. However, in the last case S3 and S4 nerve stimulation gave equal results and the S4 nerve appeared larger than usual. Initial concern over the risk of too extensive denervation was the reason for unilateral S3 neurectomies in our first 2 patients; however, one of these patients had a rapid return of symptoms and responded to division of the contralateral S3 nerve. We have not seen any example of too extensive denervation and in subsequent cases have divided at least S3 bilaterally, except for the apparently post-fixed sacral cord of the last patient, where bilateral S4 and left S3 divisions were performed. Diokno *et al.* (1977) performed only right-sided rhizotomies in an apparently comparable group of patients with satisfactory results reported on short-term follow-up, but our experience leads us to recommend bilateral neurectomies to produce better results with no appreciable side effects. We do not feel that techniques of nerve rootlet micro-dissection and stimulation which have been described for bladder denervation (Rockswold *et al.*, 1978; Toczek *et al.*, 1978) are necessarily an advantage; indeed it is of interest that Rockswold *et al.* (1978) found that their results were better when their technique of nerve stimulation and division were less selective.

Indications

Our series included patients with a variety of indications for the procedure. Successful results followed selective sacral neurectomy to aid continence and reduce frequency and urgency in patients with detrusor instability whether associated with neurological disease or not. It is to be emphasized that all of these patients had failed to respond to conservative therapy and we do not feel that the procedure is warranted in patients who have not been treated with anticholinergics. The procedure was also effective in allowing the retention of urethral catheters in patients who could not previously be managed with them.

Contraindications

The 2 failures in the series are instructive and we consider they constitute mistakes in selection. In one patient (A.W.) the pre-operative urodynamic studies revealed marked detrusor-sphincter dyssynergia and although post-operatively there were no uninhibited contractions, the patient's upper tracts deteriorated rapidly, apparently due to a hypertonic filling phase which was demonstrated cystometrically. We conclude that this was due to the persistence of dyssynergic urethral activity which was not affected by the neurectomy. It would appear that in some patients with marked detrusor-sphincter dyssynergia it is only strong, uninhibited contractions which allow voiding and if these are abolished progressive urinary retention will occur. This is a much more significant problem in the male than the female, who can usually overcome a dyssynergic urethral mechanism by straining. Thus we conclude that the presence of significant detrusor-sphincter dyssynergia in a male patient is a contraindication to selective sacral neurectomy.

The other failure was in patient G.L. who had suffered from severe enuresis all his life with only mild urgency and frequency by day and no daytime incontinence. His pre-operative urodynamic evaluation showed a different result from the other patients in that to a capacity of 400 ml there was no abnormality; it was only at 450 ml bladder capacity that there was an uninhibited contraction and incontinence. Although the patient's enuretic symptoms were severe, his urodynamic studies were not equally affected. This illustrates the point made by Whiteside and Arnold (1975) that although enuresis is usually associated with detrusor instability, the 2 conditions should not be equated. We conclude that the urodynamic findings pre-operatively are of major importance in the selection of patients and that the operation is contraindicated in the absence of marked objective findings of instability.

Experience of sacral neurectomy in the management of severe detrusor instability in patients who have not responded to conservative treatment leads us to conclude that with proper selection and adequate denervation the procedure is of value. We feel that, in the choice of which nerves to divide, intra-operative stimulation is necessary but that results are improved with more extensive denervation. Pre-operative urodynamic findings should correlate with the degree of the patient's symptoms and detrusor-sphincter dyssynergia is a contraindication in the male.

Acknowledgement

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The Urological Status of 86 Females Following Spinal Cord Injury

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Summary—A review of the urological problems in 86 female spinal cord injury patients is presented. There were no urological or renal deaths. Three urinary diversions were performed. Fifty-five patients are catheter-free and 28 are managed with permanent catheter drainage. The problems of "bladder training" are presented.

Medical literature contains a great deal of data on the urological problems following spinal cord injury in the male patients. Jouse *et al.* (1964) reported on the results of bladder training in 183 female paraplegic patients. This paper reports on the urological status of 86 female patients following spinal cord injury.

Patients

All females with traumatic cord damage admitted to the Spinal Injuries Unit in Sheffield between 1961 and early 1978 have been reviewed. Prior to 1961 there were no beds for female patients on the Unit.

During the 17-year period, 110 new cord-injured females were admitted, compared with 775 male patients. No females with non-traumatic neurological lesions have been included in this series.

Of the 110 females, 24 died in the early weeks or months following injury, all of non-urological or non-renal causes. One of the 86 survivors later died following a cerebral haemorrhage almost certainly related to autonomic dysreflexia during a cystoscopy. During the same 17-year period, 13 of the 775 males died from renal failure, the commonest cause being renal amyloidosis secondary to pressure sores (Table 1).

Table 1 Spinal Cord Injury Patients 1961-1978

Total numbers	
Male	775
Female	110
Urological deaths	
Male	13
Female	0
Female non-urological Deaths	24

The age of the patients at the time of injury varied from 3.5 to 79 years; 53% of patients were aged between 10 and 29 at the time of injury.

Every patient was managed initially with an indwelling catheter, using a latex Foley catheter 18 FG with a 5 ml balloon. On the Sheffield Unit only male patients are managed with intermittent catheterisation. One patient had an ileal conduit urinary diversion performed within 6 months of injury. Fifty-seven patients became catheter-free between 2 weeks and 6 months following injury. Two of these later had urinary diversions, one an 8-year-old girl, 3 years after injury, for social reasons. The second, 3 years after injury in another hospital, for reasons not clear to us.

Fifty-five patients are catheter-free and 28 patients have been managed with permanent catheter drainage. Most patients on permanent catheter drainage use silicone catheters which are changed at 4-weekly intervals.

The patients have been classified according to the level and completeness of the neurological lesions. The largest number of patients with permanent catheter drainage (53%) is from the group with complete cervical cord lesions. Two patients with complete low cervical lesions became catheter-free. Thirteen of the 17 patients with incomplete cervical cord lesions became catheter-free (86%). Many of the patients in this group made a good neurological recovery, allowing mobility to get to the lavatory. All 4 patients with incomplete mid-dorsal lesions became catheter-free. Seven of the 16 patients with complete mid-dorsal lesions became catheter-free.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 2 Analysis of Patients According to Level and Completeness of Neurological Lesions

	Female patients	
	Catheter	*No catheter*
Cervical (comp.)	15	2
Cervical (incomp.)	2	13
Dorsal (comp.)	9	7
Dorsal (incomp.)	0	4
D/L*	2	24
Lumbar	0	8

* Dorsolumbar fractures

Only 2 of the 34 patients with low cord or sacral root lesions have permanent catheter drainage, one for purely social reasons and another, a lady of 71, subsequently transferred to geriatric accommodation (Table 2).

Permanent Catheter Drainage

Of the 28 female patients with permanent catheter drainage, only 10 are experiencing serious problems. Six patients have recurrent bouts of leakage around the catheter and 5 patients form recurrent bladder stones requiring stone crushing. Recurrent urinary infections producing constitutional upset have been a problem in only 2 patients, despite all patients having a persistent bacteriuria. Two patients with cervical cord lesions have had problems with autonomic dysreflexia, one with a fatal outcome.

Leakage of urine around the catheter is usually caused by uninhibited, reflex detrusor contractions and is usually improved by antispasmodic drugs. Ten patients in this series are currently taking Pro-Banthine or imipramine with symptomatic improvement.

Four patients had very severe symptoms of leakage, unaffected by drugs. Three of these had a chemical, partial denervation of the bladder, using extradural alcohol blocks of both third sacral nerves, with good results. One girl of 8, paraplegic from the age of 3, had bilateral selective sacral neurectomies to enable her to retain a catheter and prevent leakage.

Catheter-free Patients

The highest percentage of catheter-free patients is found in those with incomplete neurological lesions and patients with conus or sacral root damage; 89% of patients with incomplete cervical and dorsal lesions are catheter-free; 94% of patients with conus or sacral root lesions are catheter-free. Six patients made a full neurological recovery, claiming completely normal bladder function Five patients, although not making a full neurological recovery, claimed to have normal bladder function.

Only 5 of the catheter-free patients have a significant degree of urinary incontinence, despite drug therapy. Seven patients have been, or are currently being, treated with Pro-Banthine or imipramine to reduce the symptoms of frequency, urgency or incontinence.

Thirty-six patients, some with severe degrees of bladder dysfunction, have no significant problems with incontinence or bladder emptying.

Three of the catheter-free patients have had recurrent urinary infections producing constitutional upset.

Only three patients with sacral root lesions have been given drugs to improve bladder emptying, either phenoxybenzamine or Bethanecol.

Intravenous Urography

Upper tract dilatation, usually without vesicoureteric reflux, is a well recognised complication following spinal cord injury in male patients. In this series, intravenous urography has been performed at intervals from 2 to 5 years.

Only one of the non-diverted patients has impaired drainage of the upper tracts, without reflux, subsequently developing renal scarring. The remaining 82 patients have normal upper tracts on urography.

Two of the patients with ileal conduit diversions have dilated upper tracts. One patient had a staghorn stone. Two of the non-diverted patients have small, single, unilateral stones in non-dilated upper tracts. The stones have not increased in size over 5 years.

Discussion

In patients with neurological lesions that leave the sacral cord segments intact but isolated from higher centres, the detrusor develops uninhibited, unstable contractions, producing symptoms varying from frequency and urgency to complete involuntary bladder emptying with loss of sensation.

Patients with complete conus or sacral root damage have a permanent detrusor paralysis, and voiding can only be achieved by abdominal straining or bladder compression.

Since there is no satisfactory female incontinence appliance, bladder control can only be achieved by careful training of the patient. Motivation on the part of both patient and nursing staff is essential.

Patients with uninhibited reflex detrusor activity, if sufficiently mobile to get on and off a lavatory unaided, are taught regular voiding by suprapubic triggering of a detrusor contraction, reinforcing this with abdominal straining or compression. Two of the patients in this series trigger a voiding detrusor contraction using anal stimulation.

Patients with a permanent detrusor paralysis are taught regular straining and compression, usually with few problems.

The term autonomic dysreflexia is applied to the exaggerated sympathetic response seen in patients with lesions above the fourth dorsal cord segment, in response to stimulation below the level of the lesion. The exaggerated sympathetic response produces profuse sweating, bradycardia and paroxysmal hypertension which, if unrelieved, can lead to cerebral haemorrhage.

Two tetraplegic patients in this series have had severe problems with autonomic dysreflexia, one with fatal results. This occurred in a 30-year-old with a complete C.5 tetraplegia, when several hours after a cystoscopy for bladder stones she became comatose from a right frontal lobe haemorrhage and died. The second patient with autonomic problems has recurrent bladder stones from permanent catheter drainage and requires spinal anaesthesia to abolish the exaggerated sympathetic activity during endoscopy.

The problems associated with urinary diversion in spinal cord patients have been well recorded (Moeller, 1978). Only 3 patients in this series had a urinary diversion and 2 of these have complications.

From this review of 86 female spinal cord-injured patients the following conclusions are presented:

1. Voiding and continence are dependent on the level and completeness of the neurological lesion, the age of the patient and motivation of the patient to become catheter-free.
2. Despite severe neurological disability, well-motivated patients can be taught regular voiding and can remain continent.
3. In patients who have problems with incontinence and bladder emptying through reasons of immobility, age or lack of motivation, permanent catheterisation is preferable to urinary diversion.
4. In tetraplegic patients, autonomic dysreflexia during transurethral procedures is potentially lethal.
5. Upper tract complications in female cord-injured patients are rare.

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Experimental Neurogenic Disorders of the Bladder after Section of Cauda Equina

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Summary—Changes in the cystometric pattern and urethral pressure profile after surgical section of the cauda equina have been studied in a group of 20 monkeys (Macaca nemestrina).

The experimental autonomous bladder was characterised by tonic response to filling and with variable urethral dribbling incontinence but without co-ordinated detrusor activity. This pattern developed despite previous urinary diversion to prevent inadvertent overstretch of the bladder.

Deliberate "overstretch" of the autonomous bladder was not followed by loss of tonus but was associated with the development of high amplitude regular detrusor contractions which were superimposed upon a steep rising filling cystometrogram.

With urinary diversion the resting urethral pressure profiles were preserved after division of the cauda equina but were lower in amplitude after overstretch of the autonomous bladder.

Opportunities for repetitive study before and after serious injury to the central nervous system rarely present except through animal experimentation. Confusing interspecies differences have been found but recent studies in the monkey have indicated that this animal has a sacral spinal centre for micturition and provides a suitable model for the evaluation of the neurological mechanism of micturition (Murnaghan *et al.*, 1978).

The present studies in the monkey attempted to evaluate 3 fundamental concepts of neurogenic disorder of the bladder as applied in clinical practice: (1) that acute dissociation of the spinal and vesical neurones results in loss of bladder tonus; (2) that a large capacity atonic bladder may result from overstretch of the autonomous variety, and (3) that changes in urethral tonus are relevant to the variation in bladder response to central denervation.

Materials and Methods

Observations have been made upon a group of 20 female monkeys (Macaca nemestrina). Urological studies comprised cystometry and recording of urethral pressure profiles (UPP). Cystometry was carried out with infusion at 5 ml per min; profiles were recorded during constant infusion at 1.5 ml per min through a urethral catheter (5 FG) during withdrawal by a motorised trombone (Harrison and Constable, 1970).

Cystometry and profilometry required light anaesthesia by intramuscular ketamine (10 mg/kg body weight). Anaesthesia for operative procedures was induced by ketamine and maintained by closed circuit endotracheal inhalation of nitrous oxide, oxygen and halothane.

The recording techniques were standardised in 4 animals and after individual control studies the remaining 16 animals were subjected to surgical section of the cauda equina. In 8 animals urinary diversion by ureterocolic anastomosis preceded the neurosurgery to prevent uncontrolled stretching of the bladder wall.

Cauda equina section was accomplished through a dorsal midline incision with laminectomy to allow for section of nerve roots to produce a complete lesion up to L1 neural level with preservation of the spinal cord.

Attempts to overstretch the bladder were made either by direct infusion into the bladder or by induced diuresis. The effects of attempted overstretch were studied in 3 monkeys before and in 8 monkeys after cauda equina section, with and without urinary diversion.

In 3 monkeys, following urinary diversion and cauda equina section, overstretch was attempted by the infusion of 120 ml of sterile normal saline by suprapubic bladder puncture, by urethral balloon catheter or by intubated cutaneous ureterostomy. Each route was applied in one

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Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

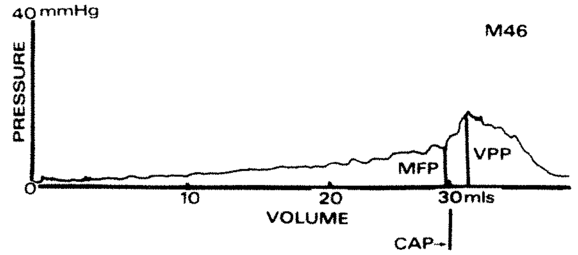

Fig. 1 Normal cystometrogram in female monkey. CAP: capacity. MFP: maximum filling pressure. VPP: voiding peak pressure.

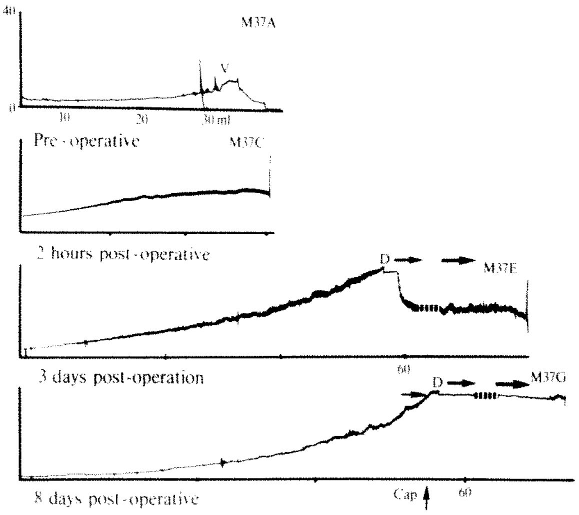

Fig. 3 Cystometrograms before and after section of the cauda equina without urinary diversion. V: voiding. D: dribbling incontinence.

animal for 3 h on 3 occasions during the first 8 days after neurosurgery.

In 5 monkeys subjected to section of the cauda equina without urinary diversion, diuresis was induced by the intravenous administration of Hartmann's solution (100 ml/h) for 3 h on the second, fourth, seventh and eighth days after neurosurgery. Frusemide (10 mg) was added to the intravenous infusion and was administered orally (20 mg) on each of the remaining post-operative days.

Cystometrograms and UPPs were obtained from each animal before and at intervals after section of the cauda equina and at intervals after attempted overstretch of the bladder. The cystometric pattern was noted and the maximum filling pressure (MFP), the voiding peak pressure (VPP) and capacity were measured (Fig. 1). The maximum amplitude of the UPP was also measured. The results were analysed in 5 groups:

1. controls,
2. cauda equina section without urinary diversion,
3. cauda equina section with previous urinary diversion,
4. cauda equina section with previous urinary diversion and with attemped overstretch of the bladder and
5. cauda equina section without previous urinary diversion but with attempted overstretch of the bladder.

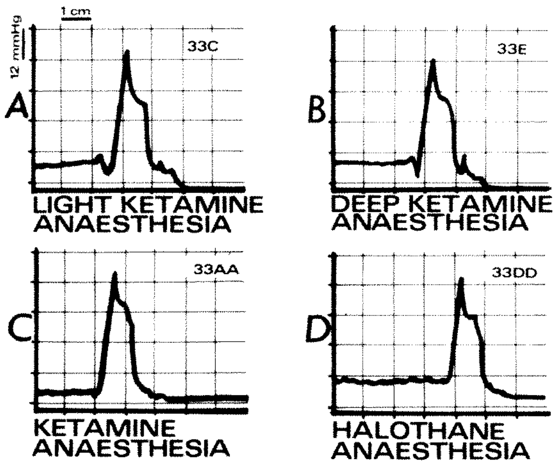

Fig. 2 Diagrams of urethral pressure profile of female monkey under (*a*) light ketamine, (*b*) deep ketamine anaesthesia on the same day and (*c*) under ketamine and (*d*) halothane anaesthesia one week later.

Results

Control Studies

In the intact monkey cystometry by either the suprapubic or urethral route showed a gradual rise in intravesical pressure to a mean MFP of 8 ± 0.8 mm Hg (mean ± SE, $n = 13$). At a mean capacity of 39 ± 4.1 ml a co-ordinated detrusor contraction produced micturition at a mean VPP of 17 ± 1.2 mm Hg (Fig. 1).

The UPP varied from animal to animal but was reproducible in the same animal under both ketamine and halothane anaesthesia (Fig. 2). The maximum amplitude of the profile varied from 20 to 85 mm Hg.

Studies of the defunctioned bladder up to 36 days after diversion showed reduction in capacity from 35 ± 7.5 ml to 22 ± 4.7 ml ($n = 5$) without significant effects upon MFP or VPP and with augmentation of the urethral profile. Endogenous diuretic overstretch had no significant effect upon any aspect of the cystometrogram. Attempts to overstretch the defunctioned bladder by suprapubic infusion produced small volume voiding at low VPP; the cystometrogram had returned to the pre-diversion normal state after 7 days.

Cauda Equina Section without Urinary Diversion

Studies within 2 h of cauda equina section in 5 of the 8 animals in this group showed an "autonomous" pattern with a steep rising cystometrogram and elevation of the MFP from a control level of 6 ± 1.3 mm Hg to 20 ± 7.1 mm Hg and an increase in bladder capacity from 37 ± 6.3 to 52 ± 11.3 ml (Fig. 3).

Later studies in each of 4 animals on the first, second, fifth and eighth day respectively after cauda equina section showed maintenance of increased capacity but with a steeper filling cystometrogram and with further elevation of the MFP from 8 ± 2.4 mm Hg to a post-operative level of 33 ± 4.3 mm Hg. Despite these high pressures coordinated micturition responses to filling were not observed (Fig. 3) but dribbling urethral incontinence generally prevailed at maintained capacity. In each of these 4 monkeys cauda equina section was followed by diminution of the UPP by a mean of 46% of the pre-operative amplitude (range 25-60%).

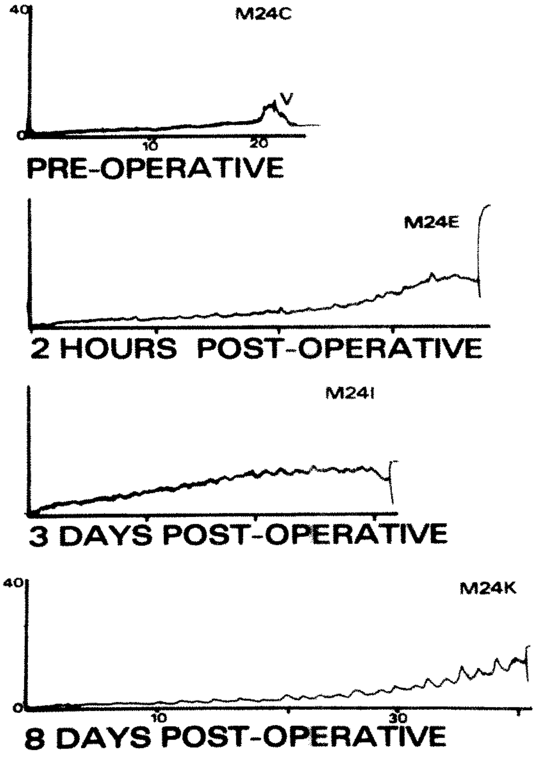

Fig. 4 Cystometrograms before and after section of the cauda equina and remote from urinary diversion.

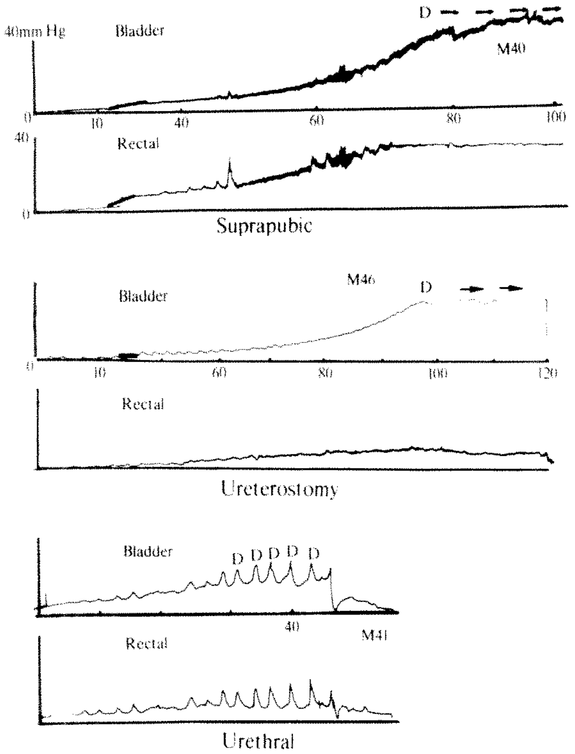

Fig. 5 Simultaneous recordings of bladder and rectal pressure after attempted overstretch of the bladder by infusion through suprapubic puncture, cutaneous ureterostomy or urethral balloon catheter in 3 separate monkeys.

Cauda Equina Section after Urinary Diversion

In this group of 7 monkeys, section of the cauda equina not less than 12 days after urinary diversion was again followed by an autonomous cystometrogram with increased capacity from 26 ± 0.4 to 41 ± 8.3 ml, and an increase in MFP from 8 ± 0.9 to 35 ± 6.5 mm Hg, in association with dribbling urethral incontinence (Fig. 4). These observations were made during periods of survival up to 20 days after neurosurgery.

In 5 monkeys of this group profilometry was recorded before and after neurosurgery. Cauda equina section did not produce any uniform change in the profiles and in 3 animals the profiles were identical before and after section during periods of observation from 8 to 20 days.

Overstretch of the Bladder after Urinary Diversion and Cauda Equina Section

There was wide variation in the response to attempted overstretch by infusion into the autonomous bladder (Fig. 5). Suprapubic infusion was followed by a 3-fold increase in bladder capacity with doubling of MFP and with a drop in the amplitude of the UPP from 30 to 10 mm Hg. A similar response was obtained from a bladder which was infused through a cannulated cutaneous ureterostomy, but there was an increase in profile amplitude from 25 to 30 mm Hg.

Attempted overstretch by infusion through a urethral balloon catheter was followed by reduction of bladder capacity from 47 to 3 ml; there was a marked drop in amplitude of the urethral profile from 22 to 10 mm Hg. Five days after overstretch, bladder capacity had returned to 47 ml with dribbling incontinence at an MFP of 15 mm Hg but with the induction of regular synchronous and similar waves in the bladder and rectum. The waves occurred twice per min with an amplitude of 10 mm Hg and a duration of 20 s (Fig. 5). The profile remained low.

Overstretch of the Bladder after Cauda Equina Section without Urinary Diversion

Attempted endogenous overstretch of the bladder after cauda equina section without previous urinary diversion was followed in each of the 5 monkeys in this group by the development of regular waves in the cystometrogram. These waves were dissociated from any variations in rectal pressure and appeared at a mean filling volume of 10±4.0 ml (n=5) and at an MFP of 10±1.3 mm Hg. They were superimposed upon a baseline plateau pressure of 14±3.5 mm Hg (n=5) with an amplitude of 11±1.6 mm Hg (n=5) and were of 20 to 30 s duration with a frequency of 2 per min (Fig. 6). The MFP as recorded at the onset of dribbling incontinence showed an increase from a control of 6±1.0 to 23±4.6 mm Hg (n=5) but was associated with a decline in effective bladder capacity from 42±6.2 ml to 27±15 ml (n=5). Dribbling incontinence did not always commence with the onset of the waves but was intermittent and coincident with them.

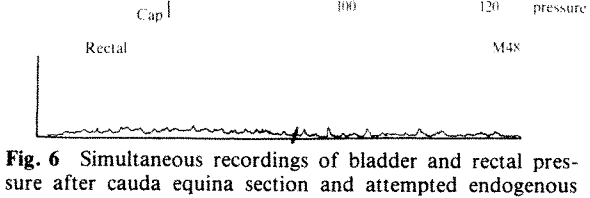

Fig. 6 Simultaneous recordings of bladder and rectal pressure after cauda equina section and attempted endogenous overstretch of the bladder.

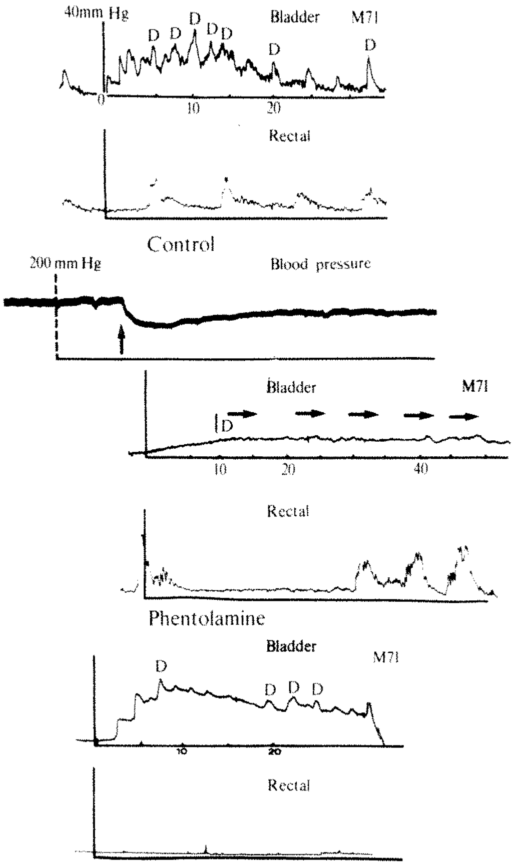

Fig. 7 Simultaneous recordings of bladder, rectal and blood pressure after cauda equina section, attempted endogenous overstretch of the bladder and the administration of phentolamine.

In one monkey with regular bladder waves and occasional irregular rectal waves it was noted that the bladder waves were abolished by the intravenous administration of phentolamine (Fig. 7) with a graduated drug dosage response. The bladder waves persisted with some modification of form and frequency after medication with atropine in a dosage sufficient to abolish rectal pressure variations (Fig. 8).

Attempted endogenous overstretch after neurosurgery with diversion was associated with diminution of the amplitude of the urethral pressure

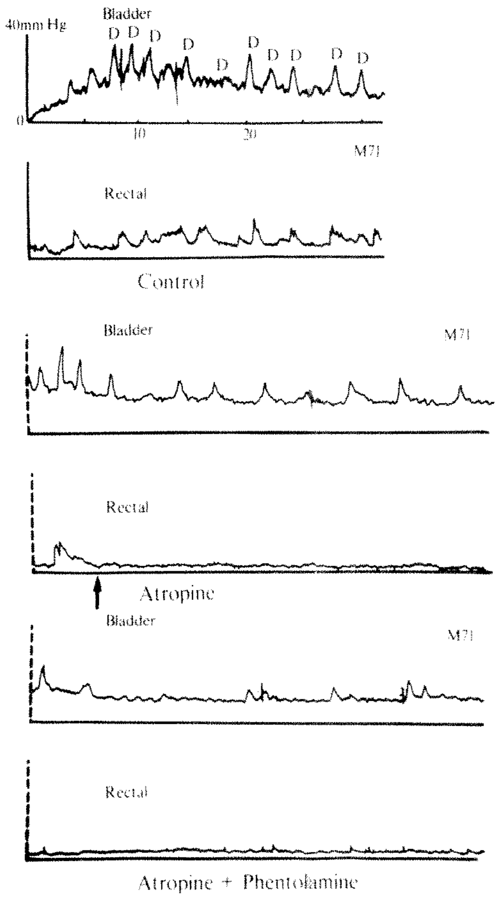

Fig. 8 Simultaneous recordings of bladder and rectal pressure after cauda equina section, attempted endogenous overstretch of the bladder and the administration of atropine and phentolamine.

profiles by a mean of 56% of the pre-section controls (range 33 to 66%: n = 4).

Discussion and Conclusions

The bladder showed a constant pattern of response to section of the cauda equina. Acute dissociation of the spinal and vesical neurones was associated with loss of the micturition response to filling but was followed by increase in both filling tonus and capacity. These changes persisted in the more chronic preparation and were not significantly influenced by previous urinary diversion. The defunctioned bladder was reduced in capacity but the mean increment after neurosurgery was identical to that of the undiverted bladder after cauda equina section.

Attempts to overstretch the autonomous bladder did not produce a large capacity atonic bladder. Direct infusion into the defunctioned autonomous bladder did not produce a uniform response but the methods were traumatic and difficult to control. Nevertheless, any increase in bladder capacity which followed direct infusion was associated with an increase in the filling pressure. Attempted overstretch of the autonomous bladder by diuretic overload was followed by an increase in filling pressure but with a cystometrogram characterised by regular superimposed waves. The dribbling incontinence associated with these waves might explain the relative reduction in functional bladder capacity. The preliminary drug studies suggested that the waves were not cholinergic but were alpha-adrenergic mediated. Such alpha-receptor activity in the detrusor muscle after parasympathetic denervation has been reported in human subjects and is in contrast to the findings in normal bladders (Norlén, 1976). In this present series of monkey experiments the possible alpha-adrenergic dependence of these waves was demonstrated at 6 days after cauda equina section. It is therefore suggested that neural adaptation or arousal of quiescent alpha-receptors in the bladder wall may provide more likely explanations of this response than the development of new alpha-receptors by adrenergic sprouting, as has been demonstrated in the cat bladder some 6 weeks after parasympathetic denervation (Sundin and Dahlström, 1973).

Previous studies in the monkey have shown that the alpha-adrenergic sympathetic system makes a major contribution to the maintenance of the urethral pressure profile (Murnaghan *et al.*, 1978). Preservation of the profile in the monkey after cauda equina section and urinary diversion and the significant depression of the profile after overstretch of the autonomous bladder suggest that a sympathetic component of the vesical plexus may mediate or modify vesicourethral integration.

Further studies after cauda equina section with ablation of the sympathetic innervation of the bladder and urethra are obviously required before bladder tonus can be attributed a non-neurogenic basis in the monkey.

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Interstitial Cystitis

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Summary—Twenty histologically proven cases of interstitial cystitis were investigated in an attempt to find evidence of a possible autoimmune mechanism in its aetiology. HLA tissue typing was performed, autoantibody profiles were obtained, and a questionnaire of the patients' past history completed, especially with respect to other autoimmune conditions. An experiment was designed to test the effect of sodium cromoglycate on rat bladders. The results are discussed in relation to the management of patients with interstitial cystitis.

Interstitial cystitis was first described by Hunner (1915) in 8 female patients as a cystitis of long duration and severe intensity, which was resistant to all forms of treatment. The aetiology has still not been established and cystodistension is the only treatment that appears beneficial; however, this only provides temporary relief. No organisms have been discovered in the urine; the histological changes are merely those of a chronic non-specific ulcerative pancystitis. One feature evident on microscopy is the presence of mast cells (Smith and Dehner, 1972) and this, together with the work of others (Silk, 1970; Gordon *et al.*, 1973) has raised the question of a possible autoimmune basis in interstitial cystitis. The occurrence of active or recurring chronic inflammation and destruction of tissue without continuing cause, such as trauma or infection, strongly suggest an autoimmune pathogenesis. These diseases, once initiated, tend to be self-perpetuating and are accompanied by frequent remissions and exacerbations. Interstitial cystitis is characterised by these features. The results we obtained from the first part of our study, taken with the work already performed by others, supports the hypothesis that interstitial cystitis is an autoimmune condition. In view of this, and the relative failure of medical treatments so far, we performed preliminary experiments to test the effect of sodium cromoglycate (Intal-Fisons), which is used in the prophylactic treatment of bronchial asthma, on normal rat bladders and on rat bladders in which we induced cystitis (Edwards *et al.*, 1978).

Methods

A questionnaire was sent out to 20 female patients with histologically proven interstitial cystitis. Similar questionnaires were also completed by 40 female patients, all over the age of 45 years, who attended the Accident and Emergency department and who had never suffered from any form of severe cystitis. This latter group acted as controls. Blood was also taken for autoantibody screening and HLA tissue typing.

The following specific information was sought in the questionnaire.

1. A history of the following diseases: rheumatoid arthritis, psoriasis and other skin diseases, multiple sclerosis, colitis, thyroid diseases, pernicious anaemia, chronic back pain, Addison's disease and recurrent eye problems.
2. A previous medical history of serious illnesses or operations.
3. Drug allergies.
4. Other allergies.
5. Family medical history.

Routine fluorescence tests for tissue antibodies with the sera diluted 1 in 5 were performed; 25 separate tissue antibodies were screened.

For the HLA tissue typing the modified NIH 2-stage complement dependent microcytotoxicity method was used and 20 antigens tested.

Finally, an experiment was designed to test the effect of different concentrations of sodium cromoglycate on normal rat bladders and then following the induction of a chemical cystitis with Cetavlon (ICI). A 2 FG epidural catheter was

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Table 1 Possible Related Conditions to Interstitial Cystitis

Condition	*Patients*	*Controls*
Thyroid disease	5	0
Herpes zoster	4	0
Psoriasis	3	1
Eye sensitivities	2	0
Rheumatoid arthritis	0	2
Coeliac disease	1	0
Colitis	1	0

*40 controls and 20 patients in series.
Positive relationship in 80% of patients in series—16.
Positive relationship in 10% of control patients—4.

passed into the rat bladder *per urethram* and the bladder emptied. It was then filled with a solution of sodium cromoglycate or Cetavlon and the solution left in the bladder for 30 min. In some animals Cetavlon was introduced prior to the sodium cromoglycate and in the reverse order in others. Some animals were sacrificed immediately; others were allowed to recover and sacrificed at 7 days. In the event of death before this time, autopsy was performed. All bladders were examined histologically after staining with haematoxylin and eosin, and Von Gieson's stains.

Results

Questionnaire

All of the patients in the series were female and post-menopausal. The mean age was 61 (youngest 47, oldest 75). The mean age of the 40 control females was 68 (youngest 45, oldest 88). The questionnaires showed that there appeared to be some possible related conditions (Table 1). There was a definite increase in the incidence of allergies, especially to drugs, compared to the control group (Table 2). A strong family history of some related diseases in comparison to the control group was also discovered (Table 3).

Table 2 Allergies Related to Interstitial Cystitis

Allergy	*Patients*	*Controls*
Drugs	14 (70%)	8 (20%)
Hayfever	6 (30%)	2 (5%)
Elastoplast	4 (20%)	1 (2.5%)
Asthma	2 (10%)	1 (2.5%)
Animals	2 (10%)	0
Allergic phenomena	28/20	12/40

Table 3 Family History in Relation to Interstitial Cystitis

Condition	*Patients*	*Controls*
Colitis	3	1
Thyroid disease	3	0
Asthma	3	1
Eye diseases	3	0
Pernicious anaemia	2	1
Rheumatoid arthritis	2	2

*40 controls and 20 patients in series

Antibody Screen

An increase in the thyroglobulin, thyroid microsomes and nuclei tissue antibodies was discovered. However, 5 patients had associated thyroid disease (7 had positive thyroid antibodies (Table 4)). No significant increase in the IgE levels was found.

HLA Tissue Typing

Although HLA 10 and 17 were present in higher proportions than in the control group, this did not quite reach statistical significance (Table 5). However, the series was small and "C" and "D" locus antigens have not yet been evaluated.

Experiment Using Sodium Cromoglycate in Rat Bladders

Sodium cromoglycate at concentrations of 1% and 2% had no histologically discernible effects on the rat bladders studied. At 4% there was an increased vascularity and undulation of the mucosa with formation of villiform processes. The induction of a chemical cystitis followed by instillation of sodium cromoglycate showed little change in the inflammatory response. However, instillation of the sodium cromoglycate prior to the induction of a chemical cystitis appeared to have protective properties in that the inflammatory response was milder, although the villiform reaction persisted.

Table 4 Positive Tissue Antibodies in Sera of Patients With Interstitial Cystitis

Tissue antibody	*Percentage positive*
Thyroglobulins	61.5
Thyroid microsomes	54.0
Nuclei	54.0
Gastric cells	23.0
Nucleoli	7.5
Smooth muscle	7.5
Reticulin	7.5

Table 5 HLA Antigens in Sera of Patients with Interstitial Cystitis and Controls

HLA antigens	*Interstitial cystitis N=28*		*Controls N=600*	
	No.	*% frequency*	*No.*	*% frequency*
Locus A				
1	6	42.8	96	32.0
2	6	42.8	151	52.0
3	2	14.3	75	25.0
9	2	14.3	58	19.3
10*	3	21.4	21	7.0
11	2	14.3	36	12.0
28	1	7.1	21	7.0
29	2	14.3	26	8.7
Blanks	4	28.6	97	32.3
Others	0	0	19	6.3
Locus B				
7	3	21.4	81	27.0
8	5	35.7	82	27.3
12	5	35.7	106	35.3
17*	3	21.4	21	7.0
18	1	7.1	15	5.0
27	1	7.1	26	8.7
W35	3	21.4	44	13.0
40	1	7.1	67	14.7
Blanks	6	42.8	119	22.3
Others	0	0		39.6

* SIG. P = 0.038.

Discussion

The cause of interstitial cystitis has remained an enigma. Our clinical observations and some of our laboratory results in patients with interstitial cystitis lend support to the hypothesis that it is an autoimmune disease. It is characterised microscopically by an infiltration of lymphocytes, plasma and mast cells and it is known that an accumulation of these immunologically competent cells is observed at some stage in all autoimmune diseases (Mackay and Burnet, 1963). Fister (1938) described the similarity of the microscopic appearance, age and sex distribution of patients with Hunner's ulcers and lupus erythematosus. Silk (1970) described an association between interstitial cystitis, thyroiditis and rheumatoid arthritis. In our series 35% had associated thyroid disease. Hand (1949) described an increased incidence of allergic reactions. Seventy per cent of our patients were allergic to drugs and other allergies were also present. The importance of mast cells in releasing factors necessary in the development of allergic and anaphylactic reactions has been demonstrated by Silk (1970), when injection of these cells into the experimental animal produced chronic inflammation and fibrosis.

An interrelation between HLA antigens and diseases in man has been reported in several diseases. Associations with HLA antigens have been described in ankylosing spondylitis, myasthenia gravis, coeliac disease, idiopathic Addison's disease, psoriasis, chronic glomerulonephritis, multiple sclerosis, hepatitis, systemic lupus erythematosus, chronic myeloid leukaemia and other diseases (Arce *et al.*, 1978). Our series was too small to show a significant increase in any of the "A" or "B" antigens but we intend to look for the "C" or "D" locus antigens in the future.

The presence of mast cells and the possible autoimmune basis for interstitial cystitis stimulated us to see whether or not sodium cromoglycate had any intravesical effect. Although it is impossible to study humans at the present time and while interstitial cystitis is very different from a chemically induced cystitis, it would seem that sodium cromoglycate has protective properties.

Autoimmune diseases are thought to occur when antibodies or immunologically competent cells are formed against components of the body. There are 2 broad categories of autoimmune disease: organ specific or disturbed antigen diseases (*e.g.* thyroiditis, atrophic gastritis) and non-organ specific or disturbed tolerance conditions (*e.g.* systemic lupus erythematosus). However, between these 2 extremes is a group of diseases characterised by organ specific damage and non-organ specific antibodies (Mackay and Burnet, 1963; Turner-Warwick and Doniach, 1965).

We are presently examining the sera of patients with interstitial cystitis for the presence of specific antibodies and by further tissue typing, as well as proceeding with our studies in the use of sodium cromoglycate. Our results so far indicate that interstitial cystitis probably is an autoimmune disease; sodium cromoglycate may provide a possible means of local treatment.

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Hibitane Bladder Irrigation in the Prevention of Catheter-associated Urinary Infection

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Summary—The effect of regular chlorhexidine bladder irrigations on catheter-induced urinary infection in patients admitted as urological emergencies was investigated. Excluding patients infected on admission the urine remained sterile throughout the period of catheterisation in 52% of those receiving chlorhexidine but in only 26% of a control group of patients.

The incidence of urinary infection in catheterised patients (Roberts *et al.*, 1965) is of particular importance in those undergoing prostatectomy for retention because the risks of operation are significantly increased in the presence of infected urine (Marshall, 1967). Any method of reducing or delaying the occurrence of infection in catheterised patients merits consideration. This study was designed to investigate the value of antiseptic chlorhexidine (Hibitane, ICI) in the prevention of urinary infection in patients after emergency catheterisation.

Patients and Methods

Male patients requiring catheterisation after emergency urological admission were introduced to the trial. They were allocated to control or chlorhexidine irrigation (test) groups by the use of a random selection table. All patients were managed by closed drainage. The test group received a twice daily instillation of chlorhexidine via the catheter. This consisted of 100 ml of a 1:2000 (0.05%) aqueous chlorhexidine solution which was retained in the bladder for 10 min before recommencing free drainage. Catheter specimens of urine (CSU) were sent for culture each morning. Those from the patients in the test group were taken before the morning chlorhexidine instillation.

Urine specimens were cultured on divided plates containing Blood and MacConkey agar, using a standard loop method. Plates were read after overnight incubation. Bacterial counts of $>10^2$/ml were detectable and all such counts were regarded as indicating bacteriuria.

For those patients who developed bacteriuria the trial ended when this was detected and the chlorhexidine instillations were discontinued in the test group patients. Otherwise each patient remained in the trial for the full period of catheterisation which was defined thus:

1. In those from whom the catheter was removed, without operation—the duration of catheterisation.
2. In those undergoing prostatectomy—until the elective removal of the post-operative catheter.
3. In those going home with a catheter *in situ* —until discharge from hospital.

Use of antibiotics was recorded but no restrictions were placed on use. Since the occurrence of bacteriuria ended participation in the trial, most antibiotic use was not relevant, although a few

Table 1 Patients in Trial: Clinical Data

	Control	*Chlorhexidine*
Total patients	63	62
Mean age	70.4 years	70.2 years
Diagnosis		
Acute retention	35	40
Chronic retention	12	14
Acute on chronic retention	7	6
Clot retention	5	1
Miscellaneous	4	1
Type of catheter		
Urethral	50	51
Suprapubic	13	11
Mean duration of catheterisation	9.6 days	9.3 days

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patients were treated before they developed bacteriuria (see below).

A standard χ^2 test was used to compare differences between groups.

Results

One hundred and twenty-five patients completed the trial, 63 in the control and 62 in the test group. The main clinical data are given in Table 1. The patients were well matched for age, type of catheter and duration of catheterisation. Although there was some imbalance in the smaller groups, the numbers in the major diagnostic categories are comparable.

Side Effects of Chlorhexidine Instillation

Three patients experienced discomfort during instillation. In one case the instillations were stopped, in the others reduction of the volume to 50 ml prevented discomfort. The urine of all 3 patients remained sterile. No other adverse effects were detected.

Urinary Infection on Admission

Twenty-five patients had bacteriuria in the initial CSU; 13 in the control group and 12 in the test group.

Infection During Period of Catheterisation

Thirteen patients in the control group and 26 in the test group maintained a sterile urine throughout the period of catheterisation. This difference was statistically significant ($\chi^2 = 7.1038$, $P < 0.01$). In Table 2 a quantitative analysis of the bacteriuria is given.

Infection in Patients Undergoing Prostatectomy

Ninety patients came to prostatectomy (Table 3). Although they were equally distributed between the 2 groups, a slightly greater proportion of those in the test group had open operations. Similar numbers in each group came to operation without having developed bacteriuria. At the elective removal of the post-operative catheter a greater proportion of the treated group than the control group still had negative urine cultures (Table 4).

Table 2 CSU Culture Results

	Control	*Chlorhexidine*
Patients with detectable bacteriuria ($>10^2$ organisms/ml)	37	24
With counts of $>10^5$ organisms/ml	24	17

Table 3 Patients in Trial: Surgical Management

	Control	*Chlorhexidine*
Total	63	62
Prostatectomy	45	45
TUR	34	27
Open	11	18
Cystoscopy	4	2
No operation	14	15
Mean delay before operation	5.4 days	5.7 days

Suprapubic Catheters

Excluding those patients with urine infected on admission, the remaining 10 control and 6 of the 10 treated patients with suprapubic catheters all developed bacteriuria.

Use of Antibiotics

Seven patients received antibiotics whilst their urine was sterile. They included patients receiving antibiotics on admission, those thought to have developed a urinary infection which was not bacteriologically confirmed, and patients receiving treatment for coincidental problems such as post-operative chest infections. Four were in the control, 3 in the test group.

Discussion

The morbidity and mortality of prostatectomy is higher in patients admitted in acute retention than in those having elective operation (Salvarlis, 1960). An important factor in this difference is the effect of infection resulting from catheterisation (Marshall, 1967). Emergency prostatectomy has rightly been abandoned. It is more difficult

Table 4 Patients Underoing Prostatectomy: Incidence of Bacteriuria

	Control	*Chlorhexidine*
Total	45	45
Bacteriuria on admission	7	8
No growth up to operation	27	31
No growth throughout catheterisation	10	17

and hazardous and these elderly, possibly unfit patients benefit from a few days pre-operative assessment (Blandy, 1976). The ideal of operation within a few days of admission cannot always be achieved, either because of the patients' medical condition or because of pressure of work in a busy unit. Suprapubic catheterisation has been advocated (Tinckler, 1967). Although our patients so treated did not have a lower infection rate they were a selected group and the numbers are small.

Antibiotic prophylaxis has been advocated for the prevention of catheter-associated infection and shown to be effective (Hills *et al.*, 1976). However, antibiotics have a number of disadvantages in comparison with local antiseptics; they are a more potent cause of side effects, they have a limited spectrum of activity, and are comparatively expensive. They may encourage the emergence and spread of antibiotic resistant strains of bacteria (Curie *et al.*, 1978).

Chlorhexidine is an effective local urinary antiseptic (Gillespie *et al.*, 1962) with low toxicity. Haematuria has been reported after its use as a bladder irrigant and prolonged instillation can cause erosive cystitis in rats (Harper and Matz, 1975). However, side effects were observed in only 3 patients in the present study and in only one patient did its use have to be stopped, despite using a higher concentration in this trial than is usual (1:2000-0.05%).

We feel that in a properly-taken catheter specimen, any level of bacteriuria must be considered significant; the quantitative limits of significance usually quoted are designed to avoid confusion caused by the inevitable contamination of a midstream specimen. Using this rigid criterion the infection rate in our patients was disturbingly high, but was significantly reduced in those patients treated with chlorhexidine. However, we were disappointed to find that we were unable to reduce the number of patients coming to operation having developed bacteriuria, although by the time of removal of the post-operative catheter the test group did show some benefit. It would appear, therefore, that chlorhexidine instillation is of more use in preventing infection acquired at or after surgery than during pre-operative catheter drainage. It should be noted that the method of instillation involved breaking the closed drainage system. Since this has proved a valuable method of preventing infection (Roberts *et al.*, 1965) the fact that infection rates in the test group were not *increased* is in itself significant. It is easier to maintain a closed drainage system before prostatectomy than after, when episodes of clot retention and the occasional need to change a catheter will inevitably occur. Thus, while interference with closed drainage may have cancelled out any benefit from the chlorhexidine before operation, this interference would be less critical postoperatively. Therefore it may be that full benefit from use of this antiseptic requires some closed method of administration. Warren *et al.* (1978) were unable to improve catheter infection rates by irrigating with a neomycin-polymyxin mixture. They likewise attributed their failure in part to increased breakage of the closed drainage in the irrigated patients.

The factors most important in preventing infection in these patients remain scrupulous technique in catheterisation, carefully supervised closed drainage systems and early operation whenever possible. Chlorhexidine instillation might prove to be a useful adjunct to these other measures.

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Vesicoplication in the Management of Chronic Urinary Retention

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Summary—Eighteen patients have been treated by vesicoplication for low tension chronic urinary retention. The clinical presentation, operative technique and results in these 18 patients are discussed. Vesicoplication is shown to be a simple, safe and effective method of relieving symptoms in this group of patients.

When the residual urine remaining in the bladder after micturition rises to a level equal to or more than the normal bladder capacity, then the patient is stated to be in chronic urinary retention (Mitchell, 1972).

Patients with chronic retention of urine show 2 distinct patterns of presentation. These can be defined as high pressure and low pressure chronic bladder retention. This distinction was described by Mitchell (1972) and subsequently confirmed and elaborated by Abrams *et al.* (1978) and is reflected in 2 quite separate modes of clinical management. In high pressure chronic retention detrusor tone is maintained, producing muscular hypertrophy and increased intravesical tension. This results in an easily palpable bladder and is usually associated with upper tract dilatation and some deterioration in renal function. These patients have convincing evidence of bladder outflow obstruction, and results of surgery are usually excellent.

In the group with low pressure chronic retention, however, there is virtually no detrusor tone demonstrable. This results in considerable distension of the bladder with no detrusor hypertrophy and makes the bladder in this group very difficult to palpate, being chiefly recognised by percussion. Though the capacity of these bladders is often in excess of 5 litres, there is usually no significant upper tract dilatation and no deterioration in renal function. As compared with the high pressure group, these patients seldom show any convincing evidence of outflow tract obstruction and surgery to the outflow tract is disappointing. It is for these patients with low pressure chronic retention, in whom surgery to the outflow tract has failed to relieve symptoms, that the operation of vesicoplication, as described originally by Stewart (1966), was devised.

Patients and Methods

Eighteen patients, 13 men and 5 women, have had vesicoplication over a 5-year period. The presenting symptoms are shown in the Table. The commonest problems were abdominal discomfort and difficulty in micturition and, in some cases, overflow incontinence. The mean duration of symptoms was 3.5 years. In each case bladder distension was difficult to detect and on one occasion was mistaken for malignant ascites. In 16 patients the urine was sterile and in 2 a coliform infection was present. In 16 patients renal function studies were normal and in 2 the blood urea was elevated, though only to 9.6 and 11.0 mmol. Excretion urography showed normal upper urinary tracts in 14 patients. In 4 there was a degree of upper tract dilatation, but this was not marked in 3 and in one was associated with infected urine and a raised blood urea. At endoscopy a degree of trabeculation was present in 13 patients, but in only 3 was this considered to be marked. All bladders had a vast

Table Presenting Features of Low Tension Chronic Urinary Retention

Reason for operation	
Incontinence	3
Difficulty with micturition	11
Abdominal discomfort	11
Chronic urinary sepsis	1
Vena caval obstruction	1

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capacity, varying from 3.5 to 8 litres. Full pre-operative and post-operative urodynamic studies were performed on 7 patients. In the pre-operative state these showed absence of detrusor function, poor flow rates and normal sphincters. All 18 patients had undergone bladder outflow surgery, but residual obstruction was considered to be present in 3 as judged by endoscopic and urodynamic studies.

Operative Technique

Three patients underwent preliminary transurethral surgery. Using either an extraperitoneal or transperitoneal approach, the bladder was mobilised out of the abdominal cavity by freeing it superiorly in the retropubic space, laterally to the level of the superior vesical vessels and posteriorly, if necessary with a patch of peritoneum, to the rectovesical space. The plication was performed using 2/0 monofilament nylon on a round-bodied needle. In the early cases 2/0 catgut was used, but this was abandoned for reasons that will be seen later. The vault of the bladder was invaginated using a series of purse-string sutures so as to produce an "ink-well" effect. The anterior and posterior walls were then plicated by a series of transverse "reefing" sutures. Alternatively, these reefing sutures were used exclusively. The stitches pierced the bladder wall only and did not enter the bladder cavity, where there was a risk of subsequent bladder stone formation. The catheter was left in post-operatively for 48 h.

Results

There has been no mortality or significant morbidity from vesicoplication in this series. At one year all 18 patients were available for review. Seventeen considered that their symptoms were relieved, but in one the symptoms had returned after 6 months. Significantly, this patient had had catgut sutures for his vesicoplication. At 2 years, 14 of the patients were available for review. Ten remained symptom-free but a further 3, all plicated with catgut, had a return of symptoms. At 5 years, 6 of the patients had been reviewed and 5 remained symptom-free and delighted with the operation. One patient still had symptoms, but he underwent a catgut plication and was the first failure at one year. The other 3 patients with failure at year 2 have subsequently undergone repeat operations using nylon and though not re-entered into these figures, they now remain symptom-free. Excretion urography has shown no alteration in upper tract appearances, apart from one patient in whom there has been some dilatation following a successful repeat vesicoplication.

Urodynamic studies in 6 patients with both pre- and post-operative studies showed no change in detrusor activity, flow rate or sphincters, simply demonstrating the marked reduction in bladder capacity, varying from 350 to 800 ml as opposed to the average of 3.5 litres pre-operatively. In one patient the post-operative urodynamic study showed a return to normal inflow cystometry, with normal detrusor activity and a residual urine of only 130 ml. He was, however, one of the 3 patients who had outflow tract surgery at the time of vesicoplication.

Discussion

It is well recognised that many patients with chronic retention have no symptoms and may never require to see a urologist. However, many of these patients do have symptoms, including abdominal discomfort, poor urinary flow or overflow incontinence, and they remain one of the most difficult problems faced by the urologist. Urodynamic studies performed on 6 patients in this series and on a much larger group in the series reported by Abrams *et al.* (1978) suggest that the reason for this chronic retention is detrusor failure, without any really convincing evidence that this is due to bladder outflow obstruction. While there may be some argument as to the cause of low pressure chronic urinary retention, it is clear that vesicoplication is a simple and uncomplicated way of providing symptomatic relief to these patients.

The reason for the success of this procedure cannot be stated with certainty, though it seems reasonable to infer that the straightforward reduction of bladder volume alone relieves the abdominal discomfort and urinary difficulty. Post-operative studies indicate that, with one exception where there was no significant detrusor activity pre-operatively, this same state of affairs persists after vesicoplication. There is little evidence to support the original contention of Stewart (1966) that there is significant detrusor activity after the operation, since this occurred in only one of the 7 patients studied urodynamically in this series. Nevertheless, symptomatic results are excellent and this procedure would seem to be useful in the management of low pressure chronic urinary retention.

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The Role of Multiple Mucosal Biopsies in the Management of Patients with Bladder Cancer

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Summary—The results of multiple biopsies from apparently non-tumour bearing bladder mucosa were studied in 154 patients with bladder cancer; 33% of the biopsies from apparently normal mucosa showed histological abnormalities including 4.5% with carcinoma. When the mucosa appeared red but flat, 52% of the biopsies showed histological abnormalities including 14% with carcinoma. Biopsies from mucosa that had a granular or mossy appearance showed carcinoma in 42%.

A more aggressive management policy was adopted in 12 patients (8%) as a direct result of the biopsy findings.

Careful examination of the bladder after cystectomy for carcinoma has demonstrated that, in a large proportion of cases, there are changes in the urothelium which, on cystoscopy, were regarded as normal. These changes range from simple hyperplasia to frank invasive carcinoma (Farrow *et al.*, 1976; Koss *et al.*, 1977; Soto *et al.*, 1977). A number of studies have also demonstrated the high incidence of urothelial abnormalities found in random biopsies from apparently normal mucosa in patients with bladder cancer (Schade and Swinney, 1968, 1973; Cooper *et al.*, 1973; Heney *et al.*, 1978; Soloway *et al.*, 1978). The influence that these findings have on prognosis and management remains uncertain.

The cystoscopic appearance of carcinoma *in situ* has frequently been described as consisting of a reddening of the mucosa, with or without a change in surface texture to give a granular, oedematous or "red mossy" appearance (Melamed *et al.*, 1964; Yates-Bell, 1971; Riddle *et al.*, 1975; Farrow *et al.*, 1976). The bladder mucosa of patients with carcinoma may show these changes either adjacent to or at a distance from the tumour. This is often interpreted on cystoscopy as representing widespread malignant change or an "unstable" urothelium. However, an associated infection, previous treatment or necrosis of tumour may all cause inflammatory changes in the bladder with a similar cystoscopic appearance.

The changes in the bladder following radiotherapy are familiar to urologists and radiotherapists and consist of mucosal pallor with varying degrees of telangiectasia. In the more severe grades of radiation reaction this may be associated with a widespread inflammatory appearance and even a granularity of the mucosa which can resemble an ulcerating or papillary tumour.

We have examined the results of multiple mucosal biopsies in patients with bladder cancer with particular reference to the cystoscopic appearance of the mucosa and the influence that these results had on patient management.

Patients and Methods

Between July 1978 and April 1979 multiple mucosal biopsies were taken from 154 patients who had a history of transitional cell carcinoma of the bladder. These patients were aged between 37 and 85 years (mean age 65 years) with a male:female ratio of 3.1:1. Biopsies were performed on (*a*) new patients who were untreated apart from a diagnostic cystoscopy and biopsy and (*b*) patients on routine endoscopic follow-up for bladder tumours treated by either radiotherapy or endoscopic diathermy with a history of recurrent tumours or with mucosal changes on cystoscopy.

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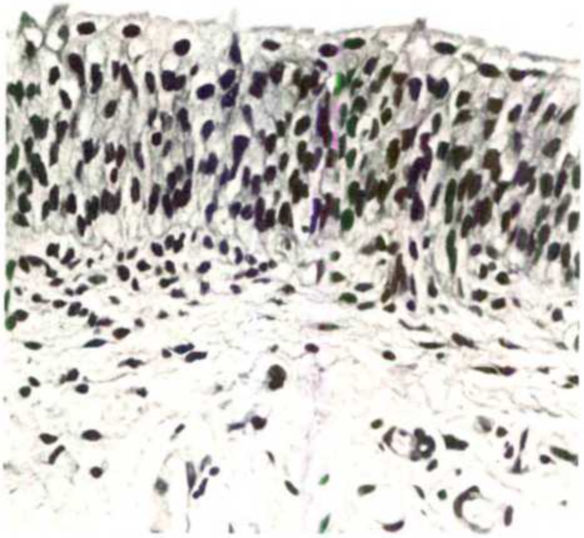

Fig. 1 Normal urothelium (H and E ×375).

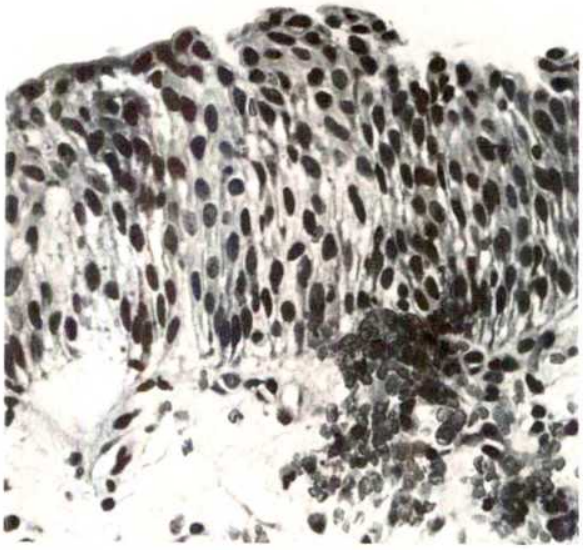

Fig. 2 Hyperplastic urothelium (H and E ×375).

Biopsies were taken with the Storz biopsy forceps from 4 pre-selected sites: the vault, the posterior wall in the midline, and 1 cm above and lateral to each ureteric orifice. Biopsies were not routinely taken from within 2 cm of a tumour.

An average of 3.8 mucosal biopsies were taken from each patient, with fewer biopsies from patients with extensive tumours or severe radiation changes. The cystoscopic appearance of each biopsy site was recorded in one of 3 categories:

1. normal,
2. flat mucosa with reddening or increased vascularity,
3. a granular, oedematous or "red mossy" appearance where the mucosa looked thickened.

The histological appearances for each biopsy were recorded in the following categories:

(1) Normal urothelium (Fig. 1): This consisted of up to a maximum of 7 cell layers; the uppermost layer was composed of occasionally binucleate flattened cells which straddled the outer epithelial cells in an umbrella fashion. In this group were also included those biopsies in which there was inflammation of the mucosa.

(2) Hyperplasia (Fig. 2): The urothelium showed an increase in the number of its component layers. There was no atypia of its component cells or nuclei. There was no increase or abnormality in mitotic activity apart from the increase in depth of the urothelial lining. Microscopic papillary projections may be present.

(3) Dysplasia (Fig. 3): Atypia of the component epithelial cells with irregularity of shape or increase in size, and hyperchromicity of the nuclei were the hallmark of this condition irrespective of the number of layers in the urothelium. In addition, there was some loss of surface orientated polarity and maturation and mitoses may be present.

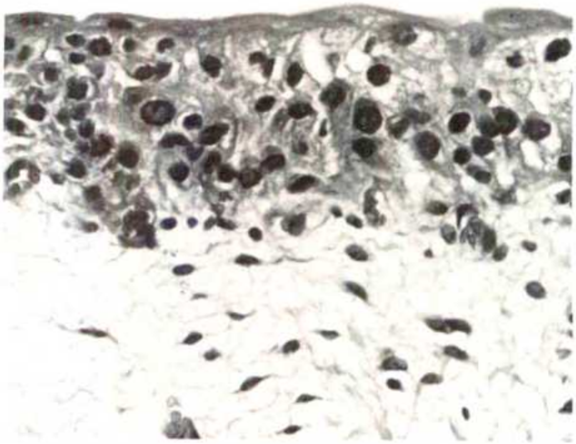

Fig. 3 Dysplastic urothelium (H and E ×375).

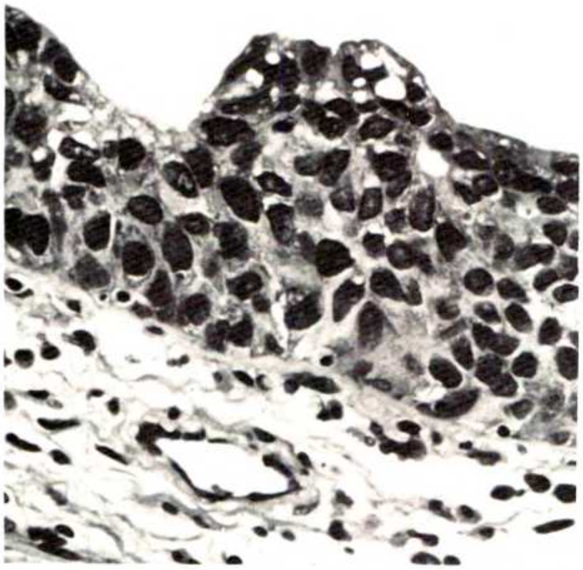

Fig. 4 Bladder urothelium: carcinoma *in situ* (H and E ×375).

These biopsies are arbitrarily subdivided into mild and severe dysplasia depending on the degree of abnormality present.

(4) Carcinoma *in situ* (Fig. 4): Irrespective of the number of layers, the urothelium in this condition was totally replaced by cells showing all of the cytological features of malignancy. Cellular pleomorphism and hyperchromatic nuclei were prominent features. Loss of stratification was complete with no residual polarity. No stromal invasion had occurred.

(5) *Frank carcinoma*, either papillary or invasive.

In the tables all carcinomas, whether *in situ* or invasive, have been grouped together.

Table 2

Previously untreated patients	56
Previous endoscopic treatment only	46
Previous radiotherapy	52
Total	154

Results

The results of all mucosal biopsies according to their cystoscopic and histological appearance are shown in Table 1. The numbers of patients in each of the 3 groups are shown in Table 2.

In 56 new patients, 34 had superficial (pTa and pT1 categories) and 22 had invasive tumours (pT2—pT4 categories). In this group of 56 patients 15 (27%) showed, on cystoscopy, some evidence of mucosal change distant from the base of the tumour. The results of the least favourable mucosal biopsy are shown in Tables 3 and 4. Tables 5 and 6 show the same data for patients previously treated endoscopically and by radiotherapy. Irradiated patients with minimal telangiectasia only were classified as having a normal mucosa.

Of the 52 patients previously treated by radiotherapy 18 had a recurrent or residual tumour on cystoscopy and 34 had no overt tumour. None of these 34 had a normal looking mucosa and 14 had either *in situ* or invasive carcinoma. In 3 cases this was invading muscle (Table 7).

In the total series, 39 patients (26%) were shown to have carcinoma in a biopsy of apparently normal mucosa. In the 24 cases where tumour was also present this was found in the nearest biopsy only to the tumour in 6 cases, but in the

Table 1 The Histology of all Mucosal Biopsies Shown According to the Cystoscopic Mucosal Appearance of the Bladder

Cystoscopic appearance	*Histological appearance*						
	Normal/ inflammation	*Hyperplasia*	*Mild dysplasia*	*Severe dysplasia*	*Carcinoma*	*Squamous metaplasia*	*Unsatisfactory biopsy*
Normal (399 biopsies)	251 (63.0%)	57 (14.0%)	38 (9.5%)	16 (4.0%)	18 (4.5%)	1 (0.25%)	18 (4.5%)
Flat red (98 biopsies)	42 (42.0%)	18 (18.0%)	11 (11.0%)	8 (8.0%)	14 (14.0%)	1 (1.0%)	4 (4.0%)
Mossy (88 biopsies)	12 (13.5%)	13 (15.0%)	12 (13.5%)	10 (11.0%)	37 (42.0%)	2 (2.5%)	2 (2.5%)
Totals (585 biopsies)	305 (52.0%)	88 (15.0%)	61 (10.5%)	34 (6.0%)	69 (12.0%)	4 (0.5%)	26 (4.0%)

Table 3 The Results of Mucosal Biopsy in 34 New Cases with Superficial Tumours Shown According to the Worst Cystoscopic Appearance of the Mucosa

Untreated patients with superficial tumours. 34 cases

Mucosal appearance	*Least favourable mucosal biopsy*				
	Normal	*Hyperplasia*	*Mild dysplasia*	*Severe dysplasia*	*Carcinoma*
Normal (27)	14	4	7	1	1
Flat red (6)	2	2	0	0	2
Mossy (1)	0	0	0	1	0

remainder it was widespread (all biopsies) or distant from the tumour. In 15 cases where no overt tumour was present this was a solitary finding in 7 cases and was widespread in 8 cases.

In this series biopsies from lesions that were thought on cystoscopy to be tumours did not always show evidence of carcinoma on histology. In patients who had not had previous radiotherapy 6.4% of biopsies were negative and for patients who had radiotherapy 10.7% were negative.

Complications

In no case was the bladder perforated by the biopsy forceps.

One patient had severe bleeding from his biopsy site requiring readmission and transfusion. Infective complications were not specifically looked for and it was not possible to assess any long-term complications.

One case deserves mention as tumour implantation mediated by the biopsy forceps may possibly have occurred. This patient had a small poorly differentiated tumour biopsied and completely resected from above his left ureteric orifice. Four random biopsies taken at the same time were entirely normal. Two months later he was found to have a 1 cm diameter solid tumour in the region of the biopsy from the posterior wall. This was also poorly differentiated and invading muscle.

Table 4 The Same Results as in Table 3 for Untreated Invasive Tumours

Untreated patients with invasive tumours. 22 cases

Mucosal appearance	*Least favourable mucosal biopsy*				
	Normal	*Hyperplasia*	*Mild dysplasia*	*Severe dysplasia*	*Carcinoma*
Normal (14)	6	1	3	0	4
Flat red (5)	1	1	0	1	2
Mossy (3)	1	0	1	0	1

Table 5 The Same Results as in Table 3 for Patients with Previous Endoscopic Treatment with Recurrences

Previous endoscopic treatment with recurrences. 46 cases

Mucosal appearance	*Least favourable mucosal biopsy*				
	Normal	*Hyperplasia*	*Mild dysplasia*	*Severe dysplasia*	*Carcinoma*
Normal (29)	17	6	3	0	3
Flat red (7)	1	1	3	0	2
Mossy (10)	0	2	2	1	5

Influence on Immediate Management

As a direct result of biopsies from apparently non-tumour bearing mucosa the following more aggressive management decisions were taken in 12 out of the 154 patients (8%).

Cystectomy	5 cases
Radiotherapy	2 cases
Intravesical Epodyl	3 cases
Earlier cystoscopic follow-up	2 cases

Discussion

The overall results of our biopsies have shown that there are frequently widespread urothelial changes in patients with bladder cancers. If the mucosa is carefully inspected, changes can be seen which, if biopsied, will yield a higher incidence of abnormalities than the cystoscopically normal mucosa. Of the biopsies from cysto-

Table 6 The Same Results as Table 3 for Patients Previously Treated by Radiotherapy

Previous radiotherapy. 52 cases

Mucosal appearance	*Least favourable mucosal biopsy*				
	Normal	*Hyperplasia*	*Mild dysplasia*	*Severe dysplasia*	*Carcinoma*
Normal (10)	3	1	4	1	1
Flat red (19)	6	5	2	1	5
Mossy (23)	1	4	4	2	12

Table 7 The Results of the Least Favourable Mucosal Biopsy in Previously Irradiated Bladders When No Tumour Was Apparent at the Time of Cystoscopy

Previously irradiated patients with no tumour present when mucosal biopsies taken. 34 cases

Mucosal appearance	*Normal*	*Hyperplasia*	*Mild dysplasia*	*Severe dysplasia*	*Carcinoma*
Normal (0)	0	0	0	0	0
Flat red (13)	6	2	1	0	4
Mossy (21)	1	4	3	3	10

scopically normal mucosa 32% showed abnormalities, with 4.5% showing carcinoma. Biopsies from mucosa that was flat and red showed abnormalities in 51% with 14% carcinoma. Where there were "red mossy" changes 81.5% were abnormal with 42% carcinoma. Thus any area of mucosal change should be biopsied, especially if the finding of carcinoma might influence subsequent management.

Following radiotherapy, areas of mucosal change as well as presumed recurrent tumour should be biopsied. Biopsies of lesions thought to be recurrent tumours after radiotherapy proved in 10.7% to be inflammatory changes with a normal, hyperplastic or dysplastic urothelium. Mucosal biopsies from irradiated bladders showed the highest incidence of carcinoma in this study. Patients with tumours recurring after previous endoscopic treatments appear to have a higher incidence of mucosal abnormalities, though a direct comparison between groups is not possible from this study.

More aggressive management decisions were taken as a direct result of the mucosal biopsy in 12 of the 154 patients (8%). Five patients had cystectomies. In 2 of these cases tumour invading muscle had been shown in a previous mucosal biopsy. The other 3 cases all had carcinoma invading the lamina propria with widespread carcinoma *in situ*. One patient with similar findings was treated by radiotherapy and one man had radiotherapy for a urothelial carcinoma involving the whole prostate. This tumour presented when a biopsy was taken from an area of mucosal change in the prostatic urethra in a man undergoing a routine follow-up cystoscopy for a well controlled bladder carcinoma.

Three patients were treated with intravesical Epodyl. Two had widespread well differentiated carcinoma without invasion of the lamina propria following radiotherapy. They both had a history of recurrent tumours but no evidence of overt recurrent tumour on cystoscopy at the time of mucosal biopsies. The third patient had recurrent tumours controlled endoscopically but was also found to have widespread carcinoma *in situ*. He was not considered to be fit for a total cystectomy.

We have regarded the finding of invasive carcinoma in the presence of widespread carcinoma *in situ* as indicating a poor prognosis and feel that the treatment of choice is a cystourethrectomy.

Two patients on yearly follow-up cystoscopy had only a single biopsy each showing well differentiated carcinoma and each patient had his next follow-up brought forward to 3 months.

The only serious complication directly attributable to the procedure of mucosal biopsy occurred in a patient who had severe bleeding from his biopsy site. This patient had previously had radiotherapy and the biopsy was from an area of severe dysplasia; he also had recurrent tumour.

The risk of tumour implantation into the biopsy site remains a theoretical hazard. There is both experimental and circumstantial evidence that tumour implantation can occur at the time of endoscopic resection and diathermy (Boyd and Burnand, 1974; Weldon and Soloway, 1975; Page *et al.*, 1978) and this may be prevented by intravesical chemotherapy at the time of cystoscopy (Burnand *et al.*, 1976; Soloway, 1977).

We conclude that the taking of multiple mucosal biopsies in patients with bladder cancer is a safe procedure and reveals an appreciable incidence of both widespread and occult carcinoma. These findings directly influenced our management in 12 (8%) of 154 patients.

Where the bladder mucosa was red or had an increased vascularity or had a granular or "red mossy" appearance there was a higher incidence of abnormalities than when the mucosa appeared cystoscopically normal.

Patients with previously untreated superficial tumours (pTa, pT1) and a cystoscopically normal mucosa had a low incidence of abnormal biopsies and in no case was management altered as a result. At present there is no good case for routine mucosal biopsy in such cases on first presentation. However, the influence that the results of mucosal biopsy have on prognosis and tumour recurrence deserve more detailed study.

The cystoscopic appearance of the bladder after radiotherapy may be difficult to interpret. Suspected recurrent tumours and areas of mucosal change should if necessary be repeatedly biopsied.

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Cystectomy for Carcinoma of the Bilharzial Bladder: 138 cases 5 Years Later

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Summary—Our experience is outlined with 138 cases of bilharzial bladder cancer treated by radical cystectomy and followed for 5 years.

The operative mortality was 13.7%. The 5-year survival rate was 32.6%. Analysis of survival figures revealed that the tumour grade was the most important prognostic factor. Most treatment failures were due to local recurrence which developed early after treatment.

It was concluded that improvement in survival might be obtained by some form of pre-operative irradiation augmented by the use of a hypoxic cell sensitiser.

Carcinoma of the urinary bladder is the commonest solid tumour among adult males in Egypt (Makar, 1955; El-Sebai, 1961). The association between bladder cancer and urinary bilharziasis determines a distinct clinicopathological behaviour. Most of the cases are seen at an advanced stage and are usually of the squamous cell type (El-Boulkany *et al.*, 1972; Ghoneim *et al.*, 1972; Khafagy *et al.*, 1972).

Radical cystectomy with urinary diversion appears to offer the best prospects for cure in most of the cases. In this paper we present the survival data and an analysis of treatment failures for cases followed up for 5 years and more.

Material and Methods

Between 1969 and 1973, 193 patients with clinically resectable bladder tumours were admitted to our department, and treated as shown in Table 1. One-stage radical cystectomy and urinary diversion were carried out for 138 patients. The age and sex distribution of this population are given in Table 2. The indications for operation were superficial tumours unsuitable for resection because of their size, and infiltrating tumours unsuitable for segmental resection in view of their size and/or location.

The extent of the radical operation was the removal of the bladder with its perivesical fat, peritoneal covering, the prostate and the seminal vesicles, together with the distal common iliac, internal iliac and external iliac lymph nodes. In the female, the bladder, urethra, uterus and upper two-thirds of the vagina with the pelvic cellular tissue and the aforementioned lymph nodes were removed. The procedure was described in a previous paper (Ghoneim *et al.*, 1972).

Table 1 Bladder Cancer Cases 1969-1973

Partial cystectomy	18
Exploration only	16
Refused operation	4
Medically unfit	3
Transurethral resection	1
Simple cystectomy	13
Radical cystectomy	138
Total	193

The various methods used for urinary diversion are given in Table 3. A rectal bladder with a terminal left iliac colostomy was most commonly employed. The justification and functional results of this technique have been reported (Ghoneim and Ashamallah, 1974).

Survival data were calculated by the direct

Table 2 Age and Sex Distribution of 138 Patients Treated by Radical Cystectomy

	Age in years					
	20-	*30-*	*40-*	*50-*	*60+*	*Total*
Males	1	14	58	22	3	98
Females	5	13	16	6	—	40
Total	6	27	74	28	3	138

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 3 Methods of Urinary Diversion

Type of diversion	*No.*	*(%)*
Rectal bladder	81	58.7
Ureterocutaneous	49	35.5
Ureterocolic	5	3.6
Gersuny-Lowsely	2	1.4
Ileal conduit	1	0.72
Total	138	

method. It was assumed that untraced patients were all dead (minimum survival rate).

Results

Nineteen patients died in hospital, an operative mortality of 13.7%. The various causes are listed in Table 4.

The distribution of cases according to clinical and pathological stages is given in Table 5. Most of the cases presented initially at an advanced stage. Moreover there was a tendency to underestimate the pathological extent of the disease, particularly at the T2 stage. Regional lymph nodes were involved in 21 cases, an incidence of 19.5%.

Table 6 shows the tumour histology and grade. Squamous cell tumours accounted for 67% of the cases, the majority of which were well differentiated.

The details of the survival figures are outlined in Table 7. The 5-year survival rate was 32.6% (with a standard error of 4% at $P=0.05$). Survival was correlated with the various pathological features (Tables 8, 9 and 10). The tumour grade appeared to be the most important prognostic factor.

Table 11 shows the distribution of causes of treatment failure (recurrences or metastasis) relative to their site and time of onset. Most of the recurrences were local in the pelvis and developed within 12 months after initiation of treatment.

Discussion

The technical principles employed were similar to those originally described by Paquin and Marshall (1956). The operative mortality of 13.7% compares favourably with other reported figures (Whitmore and Marshall, 1962; Poole-Wilson and Barnard, 1971; El-Sebai, 1977).

Table 4 Fatal Post-operative Complications

Peritonitis and adhesive ileus	9	
Septicaemia	3	
Shock	2	
Faecal fistula	2	
Cardiopulmonary complications	3	
Total	19	(13.7%)

Table 5 Clinical and Pathological Stage

	P1	*P2*	*P3*	*P4*
T1	—	—	1	—
T2	1	5	18	1
T3	1	21	71	19
T4	—	—	—	—
Total	2	26	90	20

Table 6 Tumour Histology and Grade

Histology	*Grade*		*Total*	*(%)*
	Low	*High*		
Squamous	56	37	93	67.0
Transitional	6	29	35	25.0
Adenocarcinoma	3	5	8	5.0
Sarcoma	—	2	2	1.4
Total	65	73	138	

The 5-year survival rate of 32.6% is close to the figure of 27% given by El-Sebai (1977). It is marginally lower than our previously published data (Ghoneim *et al.*, 1976), where a figure of 38.9% was reported. This could be explained by the fact that in that study, survival rate was calculated by the actuarial method.

Analysis of survival figures relative to the various pathological features of the tumour revealed that squamous and transitional tumours have essentially the same prognosis, a finding which was also reported in non-bilharzial bladder tumours by Richie *et al.* (1976). It was also demonstrated that tumour grade is the most critical prognostic index, a fact which was also emphasised by Thompson (1960).

Table 7 Treatment Results

Total number exposed to risk	138
Died post-operatively	19
Died from disease	69
Unfollowed for full period	2
Completely untraced	3
Alive at the end of 5 years	45

$$\text{Direct 5-year survival} = \frac{45}{138} = 32.6\%$$

(Standard error = 0.04)

Table 8 Survival Relative to Tumour Histology

	Squamous	*Transitional*
Total number	93	35
Died post-operatively	10	7
Died from disease	46	16
Unfollowed for full period	1	1
Completely untraced	3	—
Alive at the end of 5 years	33	11
Direct 5-year survival =	$\frac{33}{93}$ (35%)	$\frac{11}{35}$ (31%)

($P>0.05$)

The majority of treatment failures were due to local recurrence in the pelvis which developed early. These findings strongly indicate that surgical excision alone, despite being radical, was inadequate to control the local pathology. Adjuvant treatment directed to the pelvis might improve survival, and pre-operative radiotherapy seems to be the logical approach. In non-bilharzial bladder tumours, it has been demonstrated that significant improvements in survival were obtainable by combining within a planned protocol some form of pre-operative radiation followed by cystectomy (Prout *et al.*, 1971; Van der Werf-Messing, 1973; Wallace and Bloom, 1976; Whitmore *et al.*, 1977a, b).

Based on early clinical experience with external beam therapy for definitive control of carcinoma of the bilharzial bladder (Awwad, 1958), it was traditionally believed that the radioresponsiveness of these tumours is generally unfavourable. This is explained by the presence of associated bilharzial lesions which reduce the local tissue tolerance. The probability of local control is also reduced by the considerable bulk of the tumours. Furthermore, studies of the capillary vascular pattern of these tumours have documented the presence of a substantial proportion of hypoxic (radioresistant) tumour cells (Omar *et al.*, 1975).

Table 9 Survival Relative to Pathological Stage

	Superficial	*Deep*
Total number	28	110
Died post-operatively	5	14
Died from disease	10	59
Unfollowed for full period	1	1
Completely untraced	—	3
Alive at the end of 5 years	12	33
Direct 5-year survival =	$\frac{12}{28}$ (43%)	$\frac{33}{110}$ (30%)

($P>0.05$)

Table 10 Survival Relative to Tumour Grade

	Low	*High*
Total number	65	73
Died post-operatively	8	11
Died from disease	25	44
Unfollowed for full period	1	1
Completely untraced	1	2
Alive at the end of 5 years	30	15
Direct 5-year survival =	$\frac{30}{65}$ (46%)	$\frac{15}{73}$ (21%)

($P<0.01$)

Problems related to large tumour volume do not pertain to pre-operative radiation. In this setting, the aim of radiation treatment is to sterilise smaller cell burdens in the deep infiltrating parts of the tumour, as well as microextensions into the perivesical and pelvic lymphatics. Control of such foci might reduce the incidence of local recurrences which constitute the major cause of treatment failures. The remaining bulk of the tumour can be mechanically removed by cystectomy.

Considering all these factors, a prospective randomised study was initiated in our department in 1976. Two treatment modalities are compared: radical cystectomy versus 2000 rad pre-operative radiation followed by cystectomy. The radiation dose is delivered in 5 daily increments of 400 rads each. When applied to non-bilharzial bladder cancer, this regimen proved to be as efficient as others in which conventional fractionation systems were employed (Whitmore *et al.*, 1977a, b). This concentrated regimen has the potential advantage of being applicable on a large scale, since the required logistics are fairly simple, a factor of considerable importance in a country like Egypt where these tumours constitute a problem of a national magnitude.

It could be argued that the efficiency of such a concentrated regimen may be compromised by

Table 11 Treatment Failures: Distribution According to Onset and Locality

Interval (years)	*Recurrence*		*Undetermined*	*Total*
	Local	*General*		
0-	35	3	8	46
1-	10	3	1	14
2-	5	1	1	7
3-	1	1	—	2
4-5	—	—	—	—

the presence of a large proportion of hypoxic cells, the oxygenation of which could have been improved if a more protracted fractionation system was used (Kallman, 1972). Accordingly, a third arm has been recently added to the above trial. The hypoxic cell sensitiser Misonidazole (Ro-07-0582) is being used to explore its possible value in augmenting the effectiveness of preoperative radiation.

While it is too early to comment on the results of this trial in terms of survival, it is worth noting that the post-operative mortality, morbidity, average blood loss and mean hospital stay periods are essentially similar among the 3 treatment groups.

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Long-term Follow-up in Patients with Superficial Bladder Tumours Treated with Intravesical Epodyl

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Summary—Sixty-four patients with multiple, superficial papillary bladder tumours which had ceased to be controlled by endoscopic resection and diathermy were treated before July 1972 with intravesical Epodyl instillations. Of these, 19 developed no further recurrences; 20 patients were free of tumour to one year, but later developed recurrences. Twenty-four patients were never entirely free of tumour after starting Epodyl and one patient became free of recurrences 2 years after starting Epodyl. Only the patients whose histology showed no invasion of the lamina propria responded to treatment. The overall 5-year survival rate was 66%, with a disease-free interval of 61% at one year and 25% at 5 years. Failure to clear the bladder of tumour after 12 months' treatment, or worsening of biopsy stage from PIS to Pla or Plb while on treatment, were associated with a high risk of dying of invasive tumour and in future should be used as immediate indications for radical treatment.

Superficial non-invasive bladder tumours may cause problems in management as they are often multifocal, tend to recur rapidly and are often present in large numbers. Approximately 60% of patients with superficial non-invasive bladder tumours develop multiple recurrences; 15% of patients progress to invasive tumour (Marshall, 1956; Blackard, 1971) and at least 15% need cystourethrectomy because multiple superficial recurrences cannot be controlled by cysto-diathermy. Such treatment is rather radical for a disease which for most patients does not pose a threat to life, and this has led to the search for a chemotherapeutic agent which would control and, if possible, eradicate superficial bladder tumours.

Various intravesical agents have been employed to try to eradicate widespread disease in order to avoid the need for cystourethrectomy. Of the many agents tried, the most successful and therefore the most popular have been Thio-Tepa (Bateman, 1955; Jones and Swinney, 1961; Veenema *et al.*, 1962) and Epodyl (Abbassian and Wallace, 1966; Riddle and Wallace, 1971; Riddle, 1973).

Intravesical Epodyl was introduced by Abbassian and Wallace in 1966, but the first big series was not reported until 1973 (Riddle, 1973). This showed an initial good response at 3 months in 97% of patients and showed that 78% were still under control at one year. We review here the long-term results of this first series

Patients and Methods

Sixty-four patients were treated with intravesical instillations of Epodyl before July 1972 at St Peter's Hospitals, London. All patients had widespread, multiple, superficial papillary tumours which had ceased to be controlled by endoscopic resection and diathermy and had started treatment on average 4 years after initial diagnosis (range 6 months to 12 years). The instillations were of 100 ml of 1% Epodyl in distilled water which was left in the bladder for 1 h. They were given weekly for 12 weeks, then monthly for a year, and then at 3-monthly intervals. All of these patients were followed up to December 1978. The minimum follow-up period was one year and the maximum 11 years; 36 patients were followed up for more than 5 years.

Results

At one year, 39 patients were free of disease and 25 had recurrences. Of the 39 free at one year, 20 patients later developed recurrences, in 11 cases not until 2 years after starting Epodyl. Of the 25 patients with recurrences present at one year, 24 never became free of tumour; one became clear

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Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 1 The Histology in each Group at the Time of Diagnosis

	Group I	*Group II*	*Group III*	*Total*
PIS	14	14	9	37
Pla*	—	2	3	5
Plb*	—	2	5	7
PX	5	2	7	14

* Pugh (1973).

of recurrences 2 years later. If this last mentioned patient is excluded, the remaining 63 can be conveniently divided into 3 groups according to their response:

Group I Complete response to Epodyl; no further recurrences (19 patients).
Group II Responsed initially, but later developed recurrences (20 patients).
Group III Never responded to Epodyl; never free of recurrences (24 patients).

The histology of the tumours at the time of diagnosis is shown in Table 1. It can be seen that in Group I, the complete responders, no patients had evidence of invasion of the lamina propria. The mean age of the patients was similar in each group (57.7 years). It was interesting that the average time between diagnosis and starting Epodyl was significantly shorter in Group III (4.9 years) than in Group I (8 years). Understandably, the average duration of Epodyl treatment was shorter in Group III (2.8 years) than in Group I (4.7 years). We now consider that 2.8 years is much too long to leave patients on Epodyl when they have failed to respond to it.

Table 2 shows what happened to the patients in each group unrelated to time, and of note is the fact that the great majority of patients in Group III have died.

Group I (19 patients)

Eleven patients are still alive and 8 are dead. The 8 patients died from causes unrelated to their bladder tumour (5 from myocardial infarction, one from carcinoma of the stomach, one from carcinoma of the bronchus and one committed suicide). Nine patients are still receiving Epodyl.

Table 2 Long-term Results of Treatment with Epodyl, Unrelated to Time

	Group I	*Group II*	*Group III*	*Total*
Alive	11	11	6	28
Dead	8	8	17	33
Lost to follow-up	—	1	1	2

Group II (20 patients)

Eleven patients are alive, 8 are dead and one is lost to follow-up. Of the 8 who died, 7 died because of their tumour and one from carcinoma of the stomach. Fifteen patients in this group needed some radical form of therapy (9 required cystourethrectomy and 6 radiotherapy). Three are being controlled by diathermy alone and one is receiving Epodyl and having intermittent cystodiathermy.

Group III (24 patients)

Six patients are alive, 17 are dead and one is lost to follow-up. Of the 17 who died, 13 died because of their tumour and 4 from unrelated causes (1 pneumonia, 1 pulmonary embolus, 1 carcinoma of bronchus, 1 carcinoma of stomach). In this group, 19 of the 24 patients required some radical form of treatment (13 had a cystourethrectomy and 6 had radiotherapy). Only 2 of the 6 patients alive in this group retain their bladders.

The survival figures are given in Table 3. The overall 5-year survival rate was 66%. It can be seen that the 5-year survival rate was 95% in Group II, but this was probably an exceptional result, as the remaining patients who died in this group did so within the next 2 years. The 43% 5-year survival rate in the non-responders (Group III) is of interest as it can be seen from Figure 1 that up to 3 years there was no difference in the

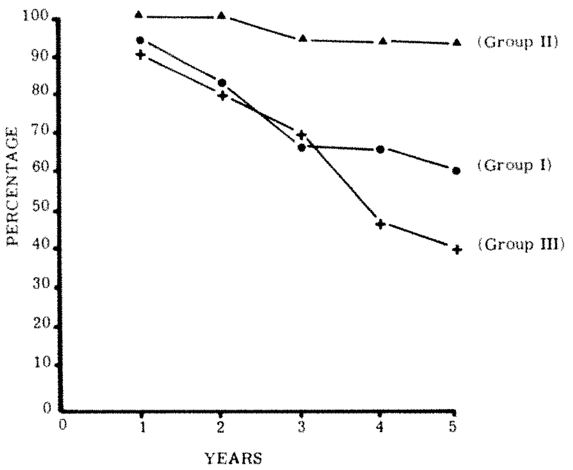

Fig. 1 The percentage survival per year in each group of patients.

Table 3 Long-term Survival in each Group. Excluded are 2 Patients Lost to Follow-up, and 1 Patient who had recurrences at 1 year, but Later Became Free of Tumour, and Therefore Did Not Fall Into Any Group

	1-year survival	*2-year survival*	*3-year survival*	*4-year survival*	*5-year survival*
Group I (n = 19)	18 (95%)	16 (84%)	13 (68%)	13 (68%)	12 (63%)
Group II (n = 19)	19 (100%)	19 (100%)	18 (95%)	18 (95%)	18 (95%)
Group III (n = 23)	21 (91%)	19 (82%)	16 (70%)	11 (48%)	10 (43%)
Total (n = 61)	58 (95%)	54 (86%)	47 (77%)	42 (69%)	40 (66%)

survival between Groups I and III, remembering that all deaths in Group I were of non-malignant disease.

The disease-free interval is given in Figure 2; 61% were free of disease at 1 year and 25% at 5 years.

Table 4 compares histology at diagnosis and just before starting Epodyl treatment in those patients who eventually underwent cystourethrectomy. In only one patient had the tumour become more invasive during the period prior to starting Epodyl. Table 5 compares histology before treatment with Epodyl and at cystourethrectomy in the same group of patients. The tumour had become more invasive in 11 of the 22 patients and lymph nodes were involved in 6 patients.

Discussion

The use of intravesical chemotherapy in patients with recurrent multiple superficial bladder tumours which are no longer controlled by endoscopic resection and diathermy is an attractive alternative to cystourethrectomy. The 5-year survival rate of this series (66%) was similar to that found by Whitmore *et al.* (1977), who performed cystourethrectomy with or without radiotherapy and reported a 67% 5-year survival rate in a series of patients with recurrent superficial tumours, although they did not mention how long patients underwent endoscopic treatment prior to cystourethrectomy.

Table 4 Comparison of the Histology at Diagnosis and Just Before Starting Epodyl in the 22 Patients Who Eventually Had Cystourethrectomy

	Histology pre-Epodyl						
Histology at diagnosis	*PIS*	*PIa*	*PIb*	*P2*	*P3*	*P4*	*PX*
PIS (11)	10	—	1	—	—	—	—
PIa (3)	1	2	—	—	—	—	—
PIb (1)	—	1	—	—	—	—	—
PX (7)	4	1	1	—	—	—	1

It is clear from the data reported here that intravesical therapy has saved some patients from cystourethrectomy and survival is certainly no worse than that achieved with cystourethrectomy alone. Whether this treatment alters the natural history of this disease or is any better than the other drugs used for intravesical treatment needs to be established by randomised studies.

Side effects from Epodyl treatment were uncommon in this study. A systemic allergic reaction in one patient and severe dysuria and frequency in a further 5 patients required treatment to be stopped. Some patients complained of frequency and urgency at the start of treatment but these symptoms usually disappeared after one or 2 weeks.

Two important lessons can be learnt from this

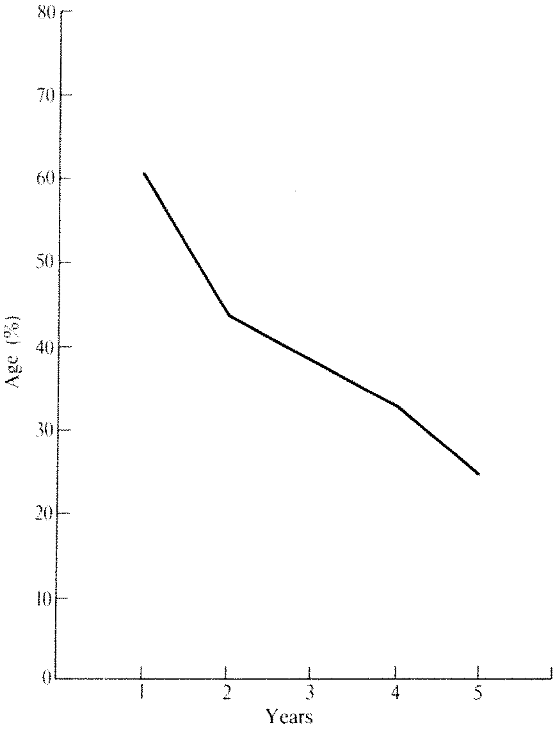

Fig. 2 The overall disease-free interval.

Table 5 Comparison of Histology Just Before Starting Epodyl and at Cystourethrectomy

	Histology of cystourethrectomy specimen						
Histology pre-Epodyl	*PIS*	*Pla*	*Plb*	*P2*	*P3*	*P4*	*PX*
PIS (15)	8	1	4	—	—	2*	—
Pla (4)	1	1	—	—	—	2†	—
Plb (2)	—	—	—	—	—	2‡	—
PX (1)	—	—	1	—	—	—	—

* 1 had no invasion through lamina propria; 1 had invasion into prostatic stroma.
† Neither patient had invasion through lamina propria.
‡ Both patients had invasion into prostatic stroma.

study. These are, firstly, that the initial response of the patient to this treatment and initial pathological biopsy staging are important prognostic indicators. Secondly, failure to clear the bladder of tumours by 12 months, or a change of histology from PIS to Pla or Plb while on treatment were associated with a poor prognosis and indicate the immediate need for radical treatment.

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The Influence of Prostatic Anatomy on the Differing Results of Prostatectomy According to the Surgical Approach

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Summary—An anatomical study of cadaver prostates has demonstrated that, in all cases, adenomatous tissue lies inferior to the verumontanum. The proportion of tissue distal to the verumontanum varies from less than 10 to 50%. In a series of 100 patients the post-operative urodynamic studies showed that in the transurethral resection group the mean urethral length was longer, the flow rate lower and the residual urine higher than in the retropubic prostatectomy group. It is suggested that prostatectomy by the transurethral route is less complete due to residual sub-verumontanal prostatic tissue. However, it is likely that by restricting resection to supra-verumontanal tissue many patients are spared post-operative stress incontinence.

The verumontanum is an important landmark in the operation of transurethral resection of the prostate. The verumontanum is thought to represent the lower limit of the prostate lobes and therefore the limit of resection of the prostate adenoma. Awareness of the risk of post-operative incontinence has led to a careful restriction of tissue resection to above the verumontanum.

Diagrams in urological texts have shown the verumontanum to lie in a variety of different positions, from the lower limit of the prostatic lobes (Blandy, 1976) to the mid-prostatic urethra (Flocks and Culp, 1975).

The relevance of the position of the verumontanum to prostatectomy led to an anatomical study of the prostate and a study of the urodynamic findings before and after prostatectomy. The results of these 2 studies are presented.

Methods

An anatomical study of the complete prostates of 28 cadavers, age 50 to 85 years, was performed. The bladder and prostate were included in the specimens removed at post mortem. The bladder was opened to demonstrate the internal meatus. The prostatic urethra was opened by an anterior longitudinal incision and the lobes separated.

A diagram of each dissected specimen was prepared (Fig. 1). Measurements were recorded of (*a*) lobe length, (*b*) lobe width, (*c*) distance from the verumontanum to the upper limit of the lobe and (*d*) the distance from the verumontanum to the lower limit of the lobe. The prostate was then divided into 4 quadrants through the apex of the verumontanum (Fig. 1) and each quadrant of adenoma dissected and weighed. The proportion

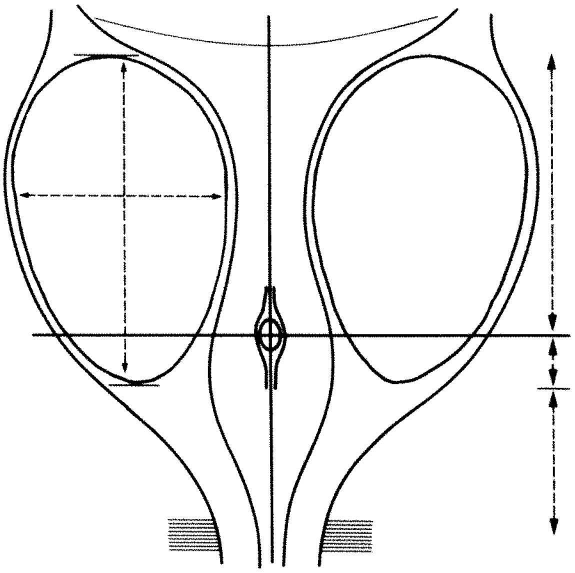

Fig. 1 Diagram to show the measurements and lines of incision used during prostatic dissection.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 1 Distribution in 28 Cadavers With Varying Percentages of Prostate Below the Verumontanum

Percentage of prostate below veru. (%)	*Percentage of patients ($n=28$)*
10	8
10-20	50
20-30	19
30-40	19
40-50	4

of tissue below the verumontanum to the total weight of the lobe was recorded.

A series of 100 patients with prostatic symptoms were assessed by urodynamic studies before and after surgical removal of the prostate. Urodynamic assessment consisted of measurement of free urine flow rate, residual urine estimation and urethral pressure profilometry. Studies were performed prior to surgery and repeated at 4 months post-operatively, by methods that have been previously described (Abrams, 1976a). In the study group 69 patients underwent transurethral prostatectomy (TUR) and 32 retropubic prostatectomy (RPP).

Results

In each dissected prostate a significant proportion of the prostatic adenoma lay below the verumontanum (Table 1). The proportion varied from 10 to 50% of the total adenoma weight. The lobes were symmetrical in the majority of dissected specimens (Table 2).

From a comparison of lobe length and lobe weight it was evident that as lobe length increases the weight increases proportionally (Table 3).

Data from urodynamic studies of these patients showed that there were significant differences between those who had undergone TUR and those who had undergone RPP. Urine flow studies showed a significantly higher maximum flow rate in the RPP group than in the TUR patients ($P<0.05$) (Table 4). Estimation of residual urine demonstrated less post-operative residual urine in the patients treated by RPP ($P<0.02$) (Table 5).

Table 2 Percentage of Prostatic Tissue Below Verumontanum

Percentage weight	
(R) lobe	(L) lobe
20.8% ±9.2	20.6% ±11.3
Total tissue (R) and (L) lobes	
21.2% ±9.53	

Table 3 Comparison of Lobe Length with Lobe Weight

Lobe length (cm)	*No. of specimens (lobes)*	*Mean weight ±S.D. (g)*
2.0	6	8.0 ±1.8
2.5	12	10.8 ±3.9
3.0	22	12.75 ±5.7
3.5	6	14.16 ±4.5
4.0	5	20.2 ±8.1
4.5	2	20.75 ±4.59

Urethral pressure profilometry showed that despite the prostatic length being greater pre-operatively in the patients subsequently treated by RPP, it was longer post-operatively in the TUR group ($P<0.01$) (Table 6). No significant difference in symptomatic results was seen in either group of patients.

Discussion

The anatomical study has shown that in most patients one can expect at least 10 to 20% of the prostate to lie inferior to the verumontanum. The urodynamic studies suggest that resectionists may leave this part of the prostate unresected. Figure 2 shows a typical response to transurethral resection. The urine flow rate has been markedly improved from 4 to 30 ml/s. The urethral pressure profile prior to surgery shows an elevated and elongated prostatic plateau depicted diagrammatically in the left lowermost illustration. After prostatectomy the urethral pressure profile changes dramatically. The pre-sphincteric part of the profile has almost disappeared: the profile catheter records bladder pressure as it is withdrawn through the open bladder neck and prostatic fossa. The difference between the 2 operative groups is seen in the part of the profile immedi-

Table 4 Average Urine Flow Rates in ml/s Before and After TUR and RPP

	Urine flow rate (ml/s)	
	TUR	*RPP*
Pre-operative	6.8 (Range 2-20)	7.7 (2-18)
Post-operative	18.4 (7-34)	23.6 (10-35)

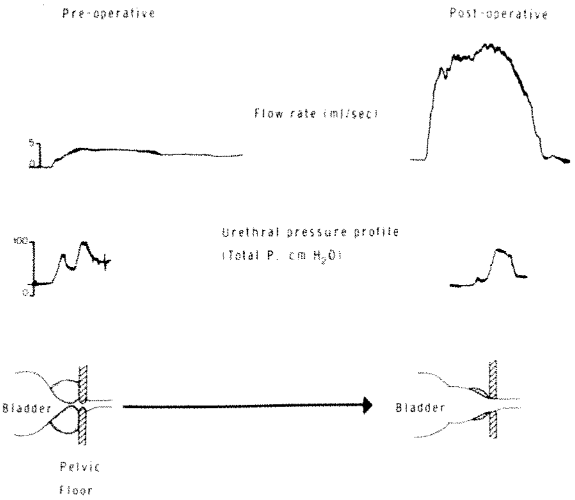

Fig. 2 Pre-operative and post-operative urine flow rates and urethral pressure profiles from a patient who underwent a transurethral resection. The 2 lowermost illustrations seek to relate the profile features to the urethral anatomy.

ately proximal to the main sphincteric peak. After retropubic prostatectomy the pre-sphincteric profile disappears completely. However, after transurethral prostatectomy the profile characteristically has a small pre-sphincteric pressure rise (Fig. 2, right-hand profile.) As indicated in the diagram beneath the profile, this rise is thought to be due to residual adenoma.

Although the urodynamic studies have shown inferior objective results after transurethral resection, the symptomatic results were no different in the 2 groups. However, symptomatic results of the transurethrally resected group suggest that the subverumontanum unresected adenoma is of no importance to the patient. A study of post-prostatectomy problems suggests that the unresected adenoma may protect some patients from stress incontinence (Abrams, 1976b). In a group of 66 patients with post-prostatectomy problems 8 patients had persistent stress incontinence. Five of these patients had had a retropubic prostatectomy. It is postulated that removal of the whole prostate, by retropubic prostatectomy, in patients with a weak pelvic floor may lead to stress incontinence, even without pre-operative damage to the sphincter.

Table 5 Average Residual Urine (ml) Before and After TUR and RPP

	Residual urine (ml)	
	TUR	*RPP*
Pre-operative	165 (Range 0-750)	284 (0-1150)
Post-operative	69 (0-370)	26 (0-100)

Table 6 Urethral Length Measured by Urethral Profilometry (cm) Before and After TUR and RPP

	Urethral length (cm)	
	TUR	*RPP*
Pre-operative	5.8 (Range 3.5-8.5)	6.4 (4.1-8.2)
Post-operative	3.2 (1.2-7.0)	2.2 (1.2-5.4)

This study suggests that the limitation of resection to above the verumontanum does not affect the symptomatic results of prostatectomy. Moreover, this incomplete prostatectomy may protect many patients from stress incontinence, particularly as there are no clear landmarks in the subverumontanal urethra, making damage to the sphincter mechanisms more likely.

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The Evaluation of 68 Patients with Post-prostatectomy Incontinence

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Summary—Sixty-eight patients with incontinence following prostatectomy for benign prostatic hypertrophy were studied. Detrusor instability was present in 45 patients, most commonly associated with sphincter damage (28 patients), but alone in 11, and with residual obstruction in 6 patients. Sphincter damage was the cause of incontinence in 47 patients (alone in 18, with detrusor instability in 28, and with residual obstruction in 3). Some abnormality was noticed in 39 of the 55 patients who underwent cystourethroscopy. All patients who complained of a combination of frequency, nocturia and urgency before prostatectomy were later found to have detrusor instability, but post-operatively no association between symptoms and pathology was noted.

It is suggested that the need for surgery should be definitely established in patients who present with equivocal symptoms. All patients with a combination of frequency, nocturia and urgency should have a urodynamic assessment before prostatectomy.

The majority of patients who undergo transurethral or open prostatectomy are symptomatically relieved by their operation. Unfortunately a small proportion become incontinent and although this distressing symptom is temporary in most patients, it persists in a small but significant percentage.

Even in those patients in whom the element of obstruction can be shown to have been relieved by prostatectomy, pre-existing detrusor instability may cause a continuation of symptoms and the appearance of disabling incontinence, despite the maintenance of a normal distal sphincter.

The importance of the role of the distal sphincter in maintaining urinary continence following prostatectomy is well established. There has been a tendency to underestimate the contribution of the bladder pressure component to incontinence. Our approach to the evaluation of post-prostatectomy incontinence is described in this study and the importance of both factors is stressed.

Patients and Methods

Sixty-eight patients with urinary incontinence following prostatectomy for benign hypertrophy were referred over a 34-month period. Transurethral resection of the prostate had been performed in 47 patients (weight range 1 to 35 g) and open prostatectomy, either retropubic or transvesical, in 21 (weight range 1 to 80 g). More than one operation had been performed in 14 patients and a further 9 had complications at the time of surgery (reoperation for haemorrhage in 6 and extravasation due to a capsular tear in 3). Pre-existing neurological problems were present in 9 patients: 4 had had an abdominoperineal excision of the rectum, 2 were diabetic, 2 had a past history of intervertebral disc prolapse, and one had had previous spinal trauma.

All patients had micturating videocystography with synchronous pressure-flow measurements. Endoscopic inspection of the urethra, prostatic cavity and bladder was carried out in 55 patients. Special note was made of the presence of urethral strictures, mucosal irregularities distal to the verumontanum and residual prostatic adenoma.

Table 1 The Length of Time Between Operation and Urodynamic Studies

<6 months	4
6-11 months	14
12-18 months	20
>18 months	30
Total	68

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 2 The End Filling Pressures

<20 cm H_2O	23
20-29 cm H_2O	7
30-39 cm H_2O	10
40-49 cm H_2O	12
50+ cm H_2O	16
Total	68

Results

Urodynamic Findings

In 50 cases the investigation was performed one year or more after the operation which rendered them incontinent (Table 1). The end filling pressures are shown in Table 2. Unstable detrusor contractions on filling were noted in 24 patients.

A peak flow rate was estimated at the time of the videocystometrogram. This was less than 15 ml/s in 23 patients, 15 to 20 ml/s in 20, and greater than 20 ml/s in 21. It was technically impossible in 4, due either to the patient's inability to void, or to leakage around the catheter on filling, associated with gross instability.

Endoscopic Findings

Cystourethroscopy was performed in 55 patients and was normal in only 16 (Table 3). Strictures were found in 17 patients, but some of these were of only filmy consistency. Residual prostatic adenoma and irregularities of the membranous urethra were found in equal numbers in both stable and unstable groups, but in a higher percentage of the patients with normal detrusor function. All of the patients with mucosal irregularities in the region of the verumontanum were independently shown to have sphincter weakness. However, 15 patients with detrusor instability and sphincter weakness, and 4 patients with sphincter damage alone had a normal membranous urethra.

Table 3 The Findings at Endoscopy, Which Was Performed in 55 Patients

Endoscopic Findings	*Urodynamic findings*		
	Unstable	*Stable*	*Total*
Normal	12	4	16
Stricture	10	7	17
Residual adenoma	5	5	10
Membranous urethral irregularity	13	14	27

Table 4 The Causes of Post-prostatectomy Incontinence in the 68 Patients

Sphincter damage alone	18
Detrusor instability alone	11
Sphincter damage + detrusor instability	26
Sphincter damage + residual obstruction	1
Detrusor instability + residual obstruction	6
Residual obstruction alone	1
Sphincter damage + detrusor instability + residual obstruction	2
No cause found	3
Total	68

Causes of Incontinence

The causes found for the patients' symptoms are shown in Table 4. Detrusor instability was defined as an end filling pressure of greater than 20 cm H_2O, with or without unstable detrusor contractions on filling. Sphincter damage was diagnosed when the patient was unable to arrest micturition at videocystography.

In most cases the patients' symptoms were due to more than one cause. Sphincter damage was present in 47 patients, with detrusor instability in 28, and alone in 18. It was associated with residual obstruction in 3 patients (2 due to residual adenoma, one due to distal sphincter dyssynergia).

Detrusor instability was present in 45 patients: alone in 11, with sphincter damage in 28, and with residual obstruction in 6 (residual adenoma in 5, distal sphincter dyssynergia in one). Residual obstruction was present in 10 patients.

Most patients (45 out of 68) had detrusor instability, but this was more commonly associated with sphincter damage than present on its own.

Symptoms

The symptoms which patients complained of before and after prostatectomy are shown in Figures 1 and 2 in order of frequency and related to detrusor function. The 16 patients with detrusor instability who complained of urgency preoperatively also complained of frequency and nocturia, whereas the 3 patients with urgency who had normal detrusor function did not complain of these symptoms.

Pre-operatively, frequency and nocturia were more commonly in the patients who had detrusor instability (67%) than in those who had not (50%). The greatest difference was with the

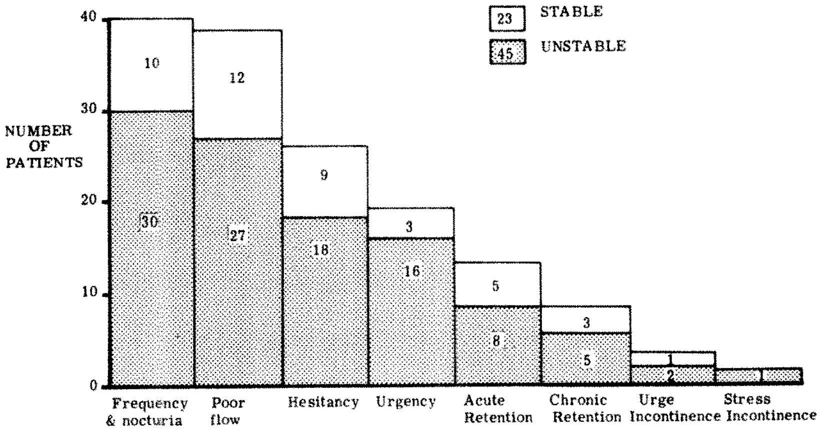

Fig. 1 The symptoms of the 68 patients before their initial operation.

symptom of urgency: 36% of the unstable group compared with only 15% of the stable group. Poor flow, hesitancy and acute retention were equally commonly seen in both groups of patients.

It was not so easy to predict the cystometrographic findings from the post-operative symptoms. Stress incontinence occurred more frequently in the patients who did not have detrusor instability (70%) than in those who did (56%). Surprisingly, nocturnal incontinence was slightly more common in the stable group (45%) than in the unstable group (33%). Otherwise no post-operative symptom was more frequently complained of by patients with normal or abnormal detrusor function.

Discussion

The maintenance of urinary continence is dependent on the urethral resistance exceeding the detrusor pressure. There are 2 separate sphincter mechanisms: the internal, or bladder neck sphincter, and the distal sphincter mechanism, which is sited partly in the membranous urethra and partly in the area of the verumontanum (Bates and Corney, 1971). This consists of an extrinsic voluntary and an intrinsic involuntary component. Three elements contribute to the latter: smooth muscle in the urethral wall, abundant elastin and collagen, and the turgor of blood vessels in the urethral submucosa (Tulloch, 1974; Gosling, 1979).

The bladder neck sphincter is destroyed at both open and transurethral prostatectomy, so that continence then depends on the distal mechanism. It is known that the contribution of the external striated muscles (the extrinsic component) is considerable but cannot be sustained. Thus, alone, it

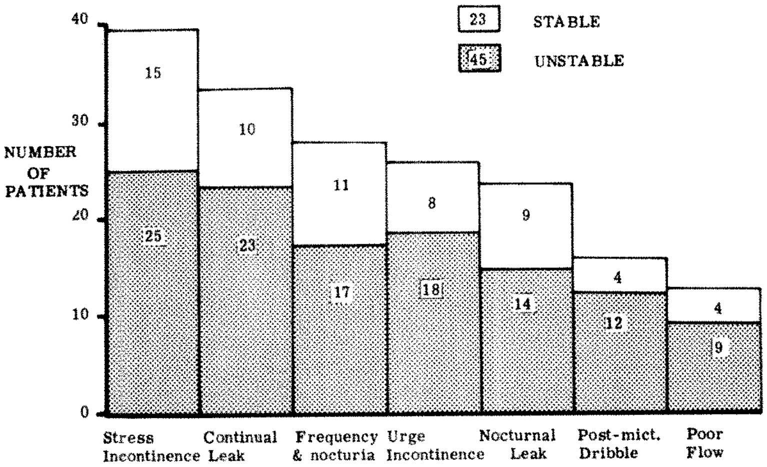

Fig. 2 The post-operative symptoms of the 68 patients, at the time of their first visit to the Urodynamic Department.

can provide continence only during a voluntary contraction. Therefore the intrinsic component, which provides passive urinary control following prostatectomy, must be preserved.

Unwanted bladder contractions are transmitted from increases in intra-abdominal pressure and, when present, inappropriate detrusor contractions. It has been pointed out that before undertaking any operative procedure directed at correcting post-prostatectomy incontinence, detrusor instability must be excluded (Turner Warwick *et al.*, 1973). We would also like to stress that all patients with equivocal symptoms should be fully evaluated before prostatectomy and the presence of obstruction verified by cineradiography. Since patients with urgency, frequency and nocturia all had detrusor instability in this series, this seems to be a particularly "at-risk" group. It is interesting to note that in the present series incontinence was due entirely to detrusor instability in 11 patients and was associated with sphincter weakness in 28 patients. It is known that continence following prostatectomy is based on a balance between the distal sphincter mechanism and the pressures achieved in the bladder during filling. If the end-filling pressure is high and the distal sphincter has been even slightly damaged, the patient may complain of incontinence.

Effective management of post-prostatectomy incontinence is directly dependent upon knowledge of both the natural history of detrusor instability following relief of obstruction as well as the individual factors contributing to each patient's incontinence. Detrusor instability associated with prostatic obstruction is reversible in most cases following relief of that obstruction. The disappearance of the instability may take up to one year and this explains the reason for withholding cystometrographic investigation for a time (Whiteside and Turner Warwick, 1976).

Endoscopic examination of the non-dynamic urethra in conjunction with the above investigations further contributes to the evaluation. Resection of residual adenoma may effect continence by removing obstruction or relieving luminal irregularities, permitting apposition of urethral mucosa in the region of the distal sphincter. It has previously been pointed out that persisting instability following prostatectomy is often due to persisting obstruction, and may be relieved by a further operation (Turner Warwick *et al.*, 1973).

This study has shown that detrusor instability was present in most patients (45 out of 68), but that sphincter weakness was present in a large number of these (28 out of 45 patients). As has been mentioned above, the sphincter weakness is always relative to the bladder pressure, and in this series 28 out of the 68 patients had very high end filling pressures (40 cm H_2O or greater).

The results of this series suggest that urgency, frequency and nocturia before prostatectomy favour detrusor instability. However, the post-prostatectomy symptoms do not correlate well with urodynamic findings. It was surprising that more patients with normal detrusor function complained of urinary leakage of urine at night than patients with instability.

We would suggest that all patients with post-prostatectomy incontinence should have a full urodynamic investigation, followed by cysto-urethroscopy. Any patient in whom there is doubt about whether bladder neck obstruction exists before prostatectomy, or in whom symptoms are equivocal, should have a urodynamic evaluation before operation.

Acknowledgements

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Prostatic Lymphoscintigraphy

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Summary—Techniques of prostatic lymphoscintigraphy using ^{99m}Tc phytate (TP) and ^{99m}Tc antimony sulphide colloid (ASC) have been evaluated in 30 patients. The most successful technique was a superficial perianal injection of ASC. In general, definition of the regional lymph nodes lacked the precision and clarity that would be required for the technique to be used in staging of prostatic or other pelvic tumours; further development of the technique is recommended.

Accurate staging of malignant tumours not only enhances our understanding of the behaviour of the tumour but also enables the clinician to plan the most appropriate form of treatment. The TNM system of tumour classification (UICC, 1978) enables the clinician to make separate assessments of the local tumour (T), the lymph nodes (N) and distant metastases (M), but the introduction of this system has also emphasised that the methods and accuracy of some of these assessments are limited.

The relevance of lymph node metastases in prostatic cancer is not in doubt and with increasing use of either external or interstitial forms of radiotherapy in early or locally invasive tumours, accurate nodal assessment is even more important.

The minimum requirements for the N category in prostatic cancer are clinical examination and pedal lymphography. Pedal lymphography is time-consuming, of limited accuracy and does not demonstrate the nodes of particular importance for the prostate, namely the obturator, internal iliac and pre-sacral groups. The addition of pelvic lumph node dissection, while improving the accuracy of the node assessment, is an invasive procedure which may not be justified in the older age group of patients (O'Donoghue *et al.*, 1976; Paulson *et al.*, 1979).

In this study we have evaluated the technique of prostatic lymphoscintigraphy (PLS) using a technique similar to that which has been used in the assessment of lymph nodes in breast cancer (Boak and Agwunobi, 1978; Ege, 1978).

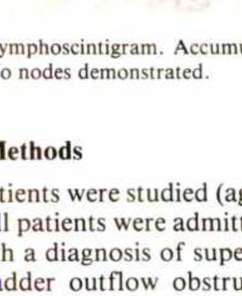

Fig. 1 Group I lymphoscintigram. Accumulation of activity within prostate. No nodes demonstrated.

Patients and Methods

Thirty male patients were studied (age 34-79 years, average 68). All patients were admitted for routine cystoscopy with a diagnosis of superficial bladder tumour or bladder outflow obstruction. A past history of pelvic radiotherapy or possible pelvic lymph node pathology excluded patients from the study.

The radiocolloid injection was carried out under general anaesthesia at the end of the endoscopic procedure. Two types of radiocolloid were used, technetium phytate (TP) and ^{99m}Tc antimony sulphide colloid (ASC). Three different injection techniques were used (Table 1).

In Group I, technetium phytate was introduced

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 1 Patients and Methods TP ^{99m}Tc Phytate; ASC ^{99m}Tc Antimony Sulphide Colloid

Group	*No. of patients*	*Radiocolloid*	*Vol. (ml) approx.*	*Injection site*	*Method*
I	5	TP	0.5	Prostatic parenchyma	Transurethral
II	8	TP	0.5	Posterior prostatic capsule	Transperineal
III	13	ASC	0.2	Posterior prostatic capsule	Transperineal
IV	4	ASC	0.2	Perianal	Superficial perianal

into each lateral lobe transurethrally using a specially designed needle attached to a 6 FG ureteric catheter. Group II patients received a transperineal injection of technetium phytate into the posterior prostatic capsular area, using an 18 gauge 3½-inch spinal needle; 0.5 ml of colloid was used in each case. In Groups III and IV, antimony sulphide colloid was used. Group III patients were injected in identical fashion to Group II and Group IV patients had a superficial perianal injection using a 21 gauge 1½-inch needle. The volume of colloid used in Groups III and IV was 0.2 ml. These injections deliver a dose of 100 to 200 μCi to the tissues. In all groups, 1500 iu of hyaluronidase in a volume of 1 ml was injected prior to the radiocolloid via the same needle.

Scanning was carried out on an Ohio-Nuclear Gamma Camera at least 3 h after injection, with a maximum time interval of 21 h.

Scans were recorded on polaroid and 10 × 8 cm conventional film, and data stored on a Varian Computer. Subsequent data processing was used to remove any non-significant scintigraphic differences from the scan, thus making the scan clearer. The photographic exposure could also be adjusted on replay of data.

Results

The results are summarised in Table 2 which shows the number of scans in each group with nodal activity and the distribution of this activity in specific nodes.

Group I scans showed an accumulation of activity within the prostate, but no nodal uptake (Fig. 1). In Group II, only 2 scans showed nodal accumulation (Fig. 2). Eight out of 13 scans in Group III showed nodal accumulation of activity (Figs. 3 and 4). Group IV was the most successful technique with 3 out of 4 scans demonstrating nodal activity (Fig. 5).

No complications attributable to PLS were detected in any of the patients studied.

Discussion

The lymphatics of the prostate have been described in detail by classical anatomists: intraprostatic lymphatics drained to the capsule of the gland, forming a periprostatic plexus which then drained into obturator, internal iliac, common iliac and para-aortic nodes. This simplistic picture has not been consistently reproduced in more recent experimental studies. Smith (1966), using vital dyes, could demonstrate drainage lymphatics only when injecting outside the capsule.

Similarly, McCullogh (1975) could not demonstrate intraprostatic lymphatics in rats using radiological techniques. Contrary evidence has recently been published by Shridhar (1979) who used several techniques, suggesting the presence of intraprostatic lymphatics and a consistent drainage pathway.

The incidence and distribution of nodal metastases in prostatic carcinoma based on pedal lymphography and pelvic lymphadenectomy have

Table 2 Results of Prostatic Lymphoscintigraphy

	Nos.	*Uptake on scanning*	*Node groups visualised*				
			Int. iliac	*Presacral*	*Inguinal*	*C. iliac*	*Para-aortic*
Group I	5	0	—	—	—	—	—
Group II	8	2	2	—	—	1	—
Group III	13	8	5	4	4	3	2
Group IV	4	3	4	—	1	2	2

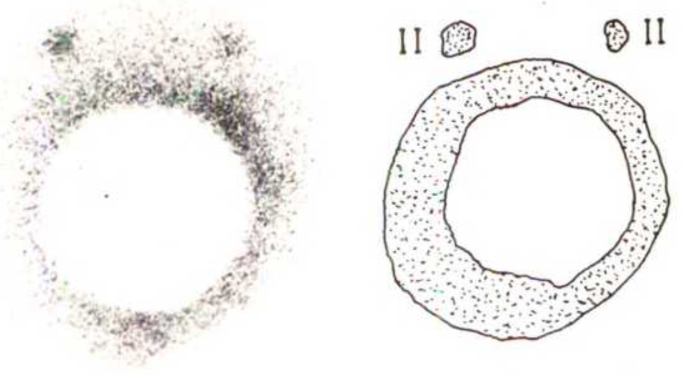

Fig. 2 Group II lymphoscintigram. Activity at injection site shielded with lead. Bilateral internal iliac (II) node accumulations.

been demonstrated by several groups (O'Donoghue *et al.*, 1976; Barzell *et al.*, 1977; Bruce *et al.*, 1977; Loening *et al.*, 1977; Paulson *et al.*, 1979).

Lymphoscintigraphy is an alternative method of demonstrating lymphatics. It depends on the injection of radiocolloids into appropriate tissue planes; direct intralymphatic injection is not required. The subsequent scan should demonstrate the function of the lymphatics rather than the distribution of a passively introduced contrast medium as in lymphography (Boak and Agwunobi, 1978; Ege, 1979).

Lymphoscintigraphy has now been evaluated in the staging and management of breast cancer. Ege (1978) has established the technique of internal mammary lymphoscintigraphy and more recently Agwunobi and Boak (1978) have described the technique of axillary lymphoscintigraphy. Although these procedures are not yet in routine practice, they remain useful adjuncts in the nodal assessment of breast cancer.

The application of lymphoscintigraphy for prostatic carcinoma would seem theoretically appropriate, with this gland's relatively inaccessible lymphatic drainage. Experimental support for a clinical study of PLS has been documented by Menon *et al.* (1977) using ^{118}Au colloid in dogs and by Tawil *et al.* (1978) with antimony sulphide colloid in rabbits.

The lymphoscintigraphic agents used in this study have been fully evaluated in experimental and clinical studies (Agwunobi and Boak, 1978; Ege, 1979). Antimony sulphide colloid is of favourably small colloidal size to induce sufficient phagocytic activity. ^{99m}Tc phytate becomes colloidal *in vivo* on precipitating with calcium ions in the tissues. Evidence suggests that ASC is at present the agent of choice (Ege, 1979).

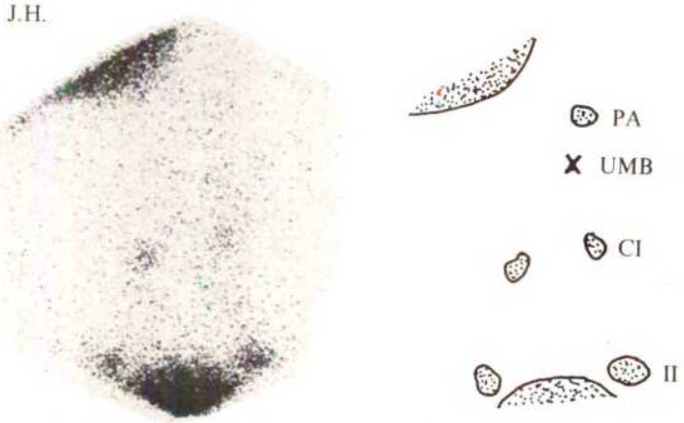

Fig. 3 Group III lymphoscintigram. II internal iliac node; CI common iliac node; UMB umbilicus; PA para-aortic node. Some activity is seen in liver at top left of scan due to spillover of colloid into circulation.

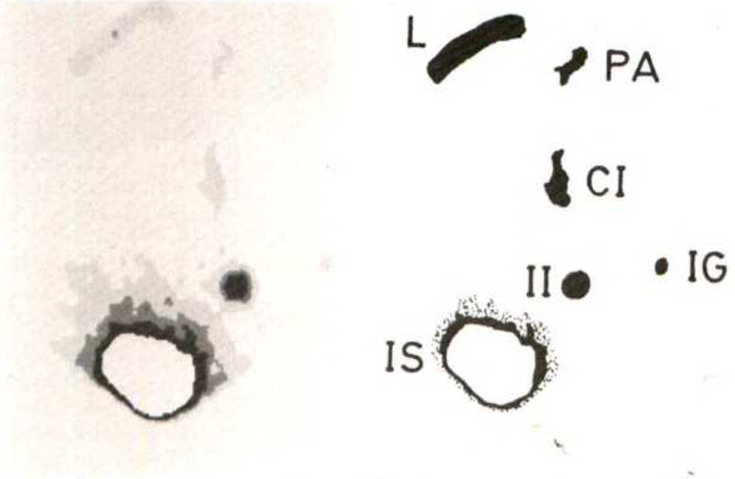

Fig. 4 Group III lymphoscintigram. After data processing. IS injection site; II internal iliac node; IG inguinal node; CI common iliac node; PA para-aortic node; L liver.

In this study, PLS has not produced scans of sufficient consistency or clarity to be of immediate routine use in the staging of prostatic carcinoma. It has demonstrated a lymphatic drainage pathway similar to that seen with other techniques. Intraprostatic injection failed to show any nodal uptake, thus again casting doubt on the existence of intraprostatic lymphatics.

The present limitations of the technique may be due to incorrect injection site or unsuitable radiocolloid characteristics.

The most consistently successful technique of PLS was a perianal injection of ASC. This method is simple, quick and safe and would merit further study. Experience with new radiocolloids may further enhance this method.

It must be emphasised that lymph node histology along with autoradiographic proof of nodal uptake has not been carried out in this study. We have yet to demonstrate the scintigraphic picture of involved nodes or nodes simply draining a prostatic carcinoma. Boak and Agwunobi (1978) suggested that depressed uptake of colloid by regional lymph nodes draining a tumour is due to local inhibition of phagocytic activity in lymph node macrophages. Ege (1979) refers to decreasing radiocolloid capacity due to tumour replacement and destruction. Increased activity may also be seen in early tumour involvement due to obstruction of flow of colloid out of the node. Thus the nature of an abnormal scan would require further definition which can only be derived from more experience with the techniques.

A suggested role of PLS in prostatic carcinoma could be to screen patients for nodal metastases. An abnormal scan might be followed by pedal

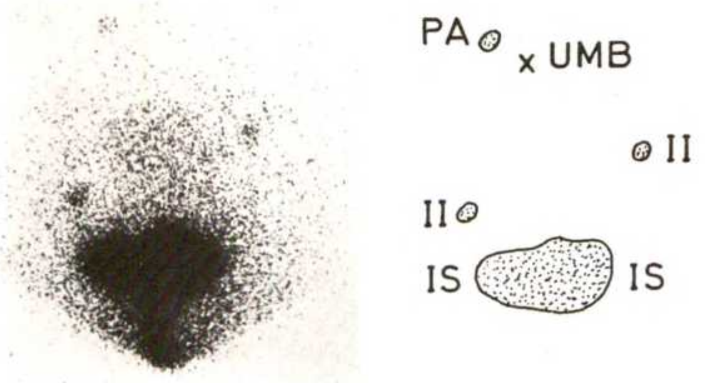

Fig. 5 Group IV lymphoscintigram. IS injection site; II internal iliac node; UMB umbilicus; PA para-aortic node.

lymphography to map the full extent of nodal disease, whereas a normal scan would obviate the need for further lymphatic investigation.

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Improved Techniques in Radionuclide Imaging of Prostatic Lymph Nodes

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Summary—Further improvements have been made in the technique of human prostatic lymphoscintigraphy, allowing better anatomical localisation of the areas of uptake of activity. A single median injection into the capsule of ^{99m}Tc labelled antimony sulphide colloid has been found to give as good imaging as 2 injections on either side of the midline. By placing markers on the umbilicus, pubic symphysis and both anterior superior iliac spines, a "pelvic grid" can be superimposed on the antero-posterior view. Further help with accurate localisation may be attained by taking 3 views; antero-posterior, postero-anterior and lateral. In 9 instances, prostatic injection was performed without any sedation or anaesthesia. The resulting scintigrams were indistinguishable in quality from those of anaesthetised patients.

There has been disagreement about the existence of lymphatics in the human prostatic parenchyma. Menon *et al.* (1977) injected ^{198}Au colloid into the dog prostate through an open bladder and showed the regional lymph nodes. Similarly, Shridhar (1979), using a range of techniques, demonstrated lymphatics in the prostate of dog and man. In contrast, Smith (1966), Rodin *et al.* (1967), Gittes and McCullough (1974) and McCullough (1975) failed to show drainage to the regional nodes when contrast medium or vital dye was injected into the prostatic parenchyma in humans. It was noted by McCullough (1975), however, that when spillage of contrast medium occurred into the prostatic capsule, the lymphatic vessels were clearly demonstrated. These findings suggest that intraprostatic lymphatics may not exist, but that there is a rich network of lymph vessels in the capsule of the human prostate.

The initial results of the search for a reliable method of demonstrating prostatic regional lymph nodes using ^{99m}Tc antimony sulphide colloid (TASC) have been previously described (Gardiner *et al.*, 1979). This study supported the view stated above. The technique for demonstrating drainage of prostatic capsular lymphatics to the regional lymph nodes is simple and the early results were encouraging, suggesting that this test could be used subsequently in the investigation of carcinoma of the prostate.

Before proceeding to such an investigation, however, it was necessary to be more certain about the anatomical location of the areas of uptake visible on the scintigram. Further experience with this technique and the efforts to improve it are described here.

Materials and Methods

In the previous communication (Gardiner *et al.*, 1979) it was described how a small dose of TASC was injected into the prostate of 25 volunteers over 55 years of age who underwent cystourethroscopic follow-up for superficial bladder tumours. These patients had not had radiotherapy nor any pelvic surgery apart from endoscopic resection of bladder tumours. Although several routes were tried, successful imaging was achieved only in those 7 patients in whom the injection was given transrectally into the prostatic capsule with a Franzen needle.

The technique has now been used on a further group of similar patients, and the improvements and modifications are described below. Scintigraphy with a Nuclear Enterprises Mark III gamma camera was performed on a further 33

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patients. All of these had transrectal injections of 0.05 to 0.10 ml (250 μCi) of TASC either as a single injection into the capsule of the prostate in the median plane or as 2 injections of 0.05 ml (125 μCi) on either side of the midline. All injections were made into the capsule of the prostate. In 9 instances midline injections were made into the prostate without any sedation or anaesthesia.

Results

A total of 40 patients has now been injected transrectally with the Franzen needle. Lymph node imaging has been possible in all patients using this method.

In the first 7 patients in whom this technique was used, injection of TASC produced patterns on the scintigram which were recognisable as lymph nodes. However, the areas of uptake of activity could not be named as a particular group of nodes with any degree of certainty. Several methods of resolving this problem have been employed.

Firstly, a single midline injection into the prostatic capsule was used. It was found that the scintigram imaging was comparable with the 2-injection site method. It was also found that although good demonstration of the lymph nodes was achieved with both modes of injection, drainage to one side more than the other occurred in most cases, irrespective of the number of injections (Fig. 1).

When markers are placed on the umbilicus, pubic symphysis and both anterior superior iliac spines, the pelvis may be mapped and a "pelvic grid" superimposed on the scintigram showing the anatomical location of the different groups of lymph nodes (Fig. 2).

It was found that scintigraphy performed at 6 h after injection did not provide better imaging than at 3 h. There was an advantage in obtaining 3 views of the patient's pelvis: antero-posterior, postero-anterior and lateral. If a group of nodes was nearer the back than the front of the patient it appeared to be more intense on the PA view and less brilliant on the AP view (Fig. 3).

In 9 cases prostatic injection was performed without any sedation or anaesthesia. This caused minimal discomfort, provided that the injection tip of the Franzen needle was withdrawn until the finger-guard had been advanced through the pain sensitive anal verge. The resulting scintigrams were indistinguishable in quality from those of anaesthetised patients.

No side effects to the radionuclide injection were experienced.

Discussion

The necessity for full and accurate staging of prostatic tumours has been stressed before, particularly in respect of the TNM classification (Wallace *et al.*, 1975). The importance of nodal metastases in carcinoma of the prostate is well

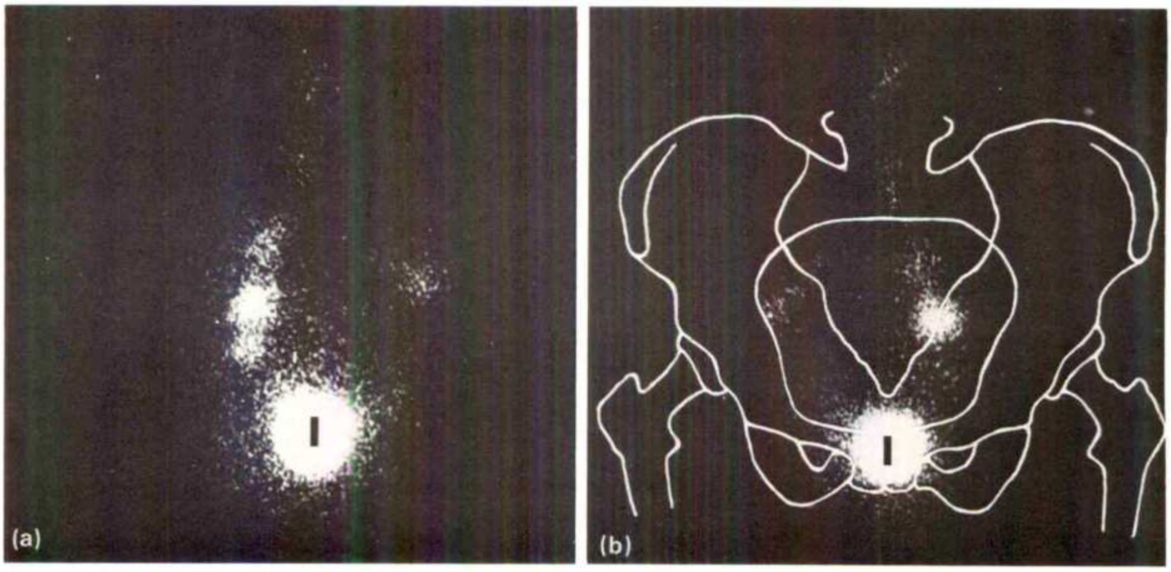

Fig. 1 (*a*) PA and (*b*) AP views showing a stronger activity in the left-sided drainage route (1 = injection site).

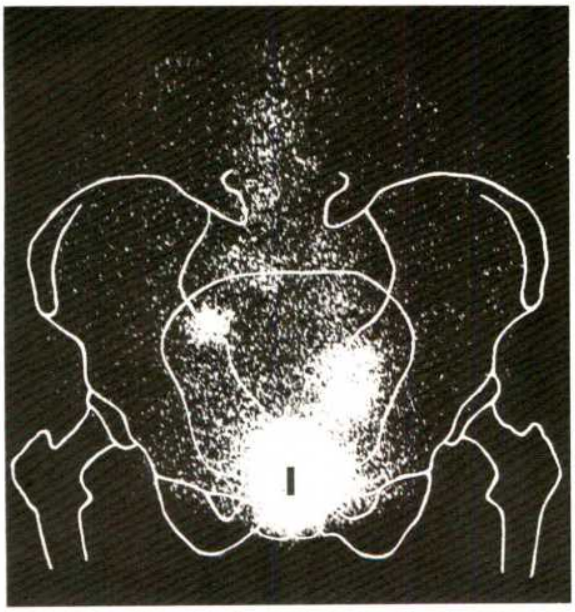

Fig. 2 AP pelvic view showing injection site (I) and a clear pattern of lymph drainage.

known (Flocks, 1973), but the difficulty in detecting nodal metastases has also been noted (O'Donoghue *et al.*, 1976). Conventional pedal lymphography has not always been totally accurate even in the most experienced hands, and demonstrates only the juxtaregional lymph nodes. Pelvic lymphadenectomy is associated with a high morbidity, but is more accurate than lymphography. Golimbu *et al.*, 1979 described the operation of extended pelvic lymphadenectomy which is, however, a long procedure with extensive dissection deep in the pelvis. Raghavaiah and Jordan (1979) have cited their experience with prostatic lymphography, but this involves the slow injection under anaesthesia of a relatively large volume of contrast medium (6-8 ml per lobe).

We have found that only in patients in whom the injection was made into the prostatic capsule was drainage into the pelvic lymph nodes demonstrated, whereas injection into the prostatic parenchyma was not associated with drainage to lymph nodes. The methods described above for improving the imaging, and for more accuracy in defining the position of the lymph nodes, have made the procedure more reliable and more information has been made available.

Our intention is to develop a test which is reliable enough to be used in patients with carcinoma of the prostate. The importance of nodal metastases in this condition is not doubted. Flocks (1973) showed a marked decrease in overall survival if the pelvic lymph nodes were involved. Spaulding and Whitmore (1978), drawing attention to the fact that there is no reliable non-invasive way of assessing nodal metastases in carcinoma of the prostate, found that regional lymph node enlargement, assessed at surgery, correlated well with bladder, rectal and seminal vesical involvement. McCullough *et al.* (1974) noted that nodal metastases were often found without evidence of concomitant bony metastases, and McLaughlin *et al.* (1976) found a high incidence of unsuspected nodal metastases in carcinoma of the prostate.

All of these reports stress the importance of nodal metastases and the necessity to obtain as much knowledge as possible about the regional lymph nodes. At present this cannot be done without surgery. With the renewed interest in radical external beam radiotherapy as a definitive treatment, the need for such a relatively non-invasive investigation is underlined. The poorer survival following total prostatectomy, if regional nodes are involved, is well known (Spaulding and Whitmore, 1978). Bagshaw *et al.* (1975) have

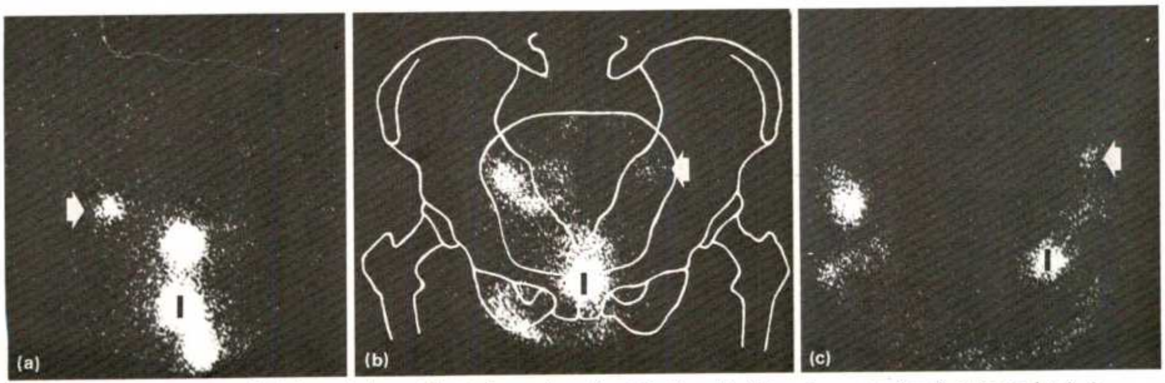

Fig. 3 (*a*) PA, (*b*) AP and (*c*) lateral views. The 3 views show the injection site (I) and serve to localise the nodes (→).

shown that the same applies to patients treated by external beam radiotherapy.

Several problems remain. Approximately 85% of the activity stays at the injection site. The resultant intense background activity interferes with definition of lymph node uptake. We have been unable to increase the amount of lymphatic drainage by applying simple methods (*e.g.* prostatic massage). Furthermore, the number of lymph nodes demonstrated has varied from minimal in some patients to the apparently complete internal iliac and para-aortic lymph node chain in others. It has also been found that better imaging of lymph nodes on one side of the pelvis usually occurs. In most cases bilateral nodes are demonstrated but visualisation of one side is often greater than the other. This is not affected by the number of injection sites used.

Nevertheless, the attractions of this investigation are that it is easily, readily and safely repeated, able to be performed in the out-patient department and should allow for quantification by computerised gamma camera techniques. With these points in mind, it is obvious that this procedure requires further development before it can be applied to patients with carcinoma of the prostate.

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Diagnosis and Staging of Prostatic Cancer by Transrectal Ultrasonography. A Preliminary Study

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Summary—Sixty men (7 normal, 53 with prostatic disease) underwent transrectal ultrasonic scanning of their prostates in order to assess the technique and evaluate its reliability in the detection and staging of prostatic cancer.

The prostatic capsule was clearly seen in 58 men; non-integrity of the capsule occurred only in those with proven cancer (17 cases). An ultrasound diagnosis of cancer was made for 32 of 33 men with proven disease and it was shown that ultrasound demonstrated anterior perforations of the capsule in 6 out of 18 men with tumours that had been judged by rectal palpation to have been confined to the prostate.

It is concluded that transrectal ultrasound is a promising technique of imaging the prostate, particularly in relation to selection of patients for biopsy and for checking staging of cancer carried out by digital assessment of the prostate.

It is generally agreed that an objective technique that can detect the presence and extent of cancer in the prostate is urgently needed. Rather surprisingly, CAT scanning and transabdominal ultrasound have proved to be disappointing in this regard (Sukov *et al.*, 1977), but recent reports from Japan about ultrasonic scanning of the prostate through the rectum have been most encouraging (Harada *et al.*, 1979).

We present our preliminary experience with transrectal ultrasonography of the prostate in which we have paid particular attention to the quality of imaging that was achieved and its reliability in the detection and staging of prostatic cancer.

Equipment, Methods and Clinical Subjects

The equipment used to scan the prostate was an Aloka ultrasound probe with a rotating 3.5 MHz transducer and this was mounted on a chair. The height and angle of the probe could be adjusted mechanically to suit the needs and comfort of each subject who was carefully guided to lower himself on to its tip so that it passed through the anal canal and entered the lower rectum. No bowel preparation was necessary. When he was sitting comfortably, the probe was then advanced into his rectum and a small balloon at its tip was inflated with water to establish continuity between the ultrasound transducer and the tissues of the pelvis. The transducer could rotate radially to give a 360° scan of the pelvis and by adjusting the level of the probe, scanning was carried out in 0.5 cm steps from the base of the bladder and seminal vesicles down to the apex of the prostate. It was therefore possible to measure this distance accurately.

The rectal probe was coupled to a Searle PhoSonic Gray Scale "B" Mode Scanner which incorporated a Digital Scan Converter and microprocessor. This combination allowed faster writing speeds that gave improved image resolution, and the images seen on the display screen were photographed for permanent record by means of a Birchover Multi format Camera Back which was attached to the equipment.

Our study was based upon prostatic scanning of 60 subjects with a total of 69 examinations (Table 1). Seven were volunteers aged from 23 to 52, including all of the authors of this study, and they were considered to have normal prostates. Fifty-three patients were grouped into those with prostates that felt enlarged and benign, those that felt malignant, and those with a nodule whose nature was in doubt. The clinical assessment of these patients was made by one observer (W.B.P.).

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Table 1 Clinical Material Details

Clinical diagnosis	*No. of subjects*	*No. of examinations*	*Histology known*
Normal	7	7	—
B.P.H.	11	11	8
Ca P	35	44	35
"Nodule" ±B.P.H.	7	7	7
	60	69	50

Radiological evidence of prostatic calcification was checked in all patients.

The study was planned so that our radiological observer (G.J.G.) had no advance knowledge of the clinical details of any patient, and he was required to make a tissue diagnosis based purely upon the features of the ultrasound scan. If he thought that cancer was present it should be staged on the evidence shown by the scan. These findings were later compared with the clinical assessment which had been previously made, and in some cases Trucut needle biopsy of the prostate was considered advisable because of the ultrasound report. Histological information was available for all patients in this series except for 3 men with benign hyperplasia who did not require surgical treatment.

Results

Ultrasonic Features of the Prostate

Normal Prostate The capsule of the prostate was represented best in scans of normal glands and it appeared as a typically crescent-shaped outline in all cases. The parenchyma of the normal prostate was represented by evenly spaced homogeneous echoes within the capsule (Fig. 1).

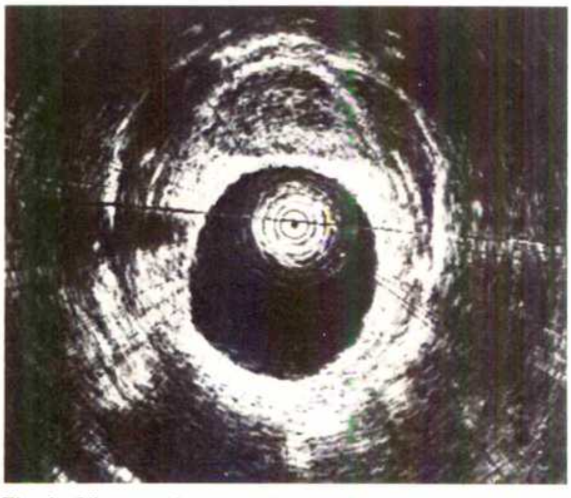

Fig. 1 Ultrasound scan of normal prostate. The Aloka probe is seen centrally within a transonic area representing the balloon filling the rectum.

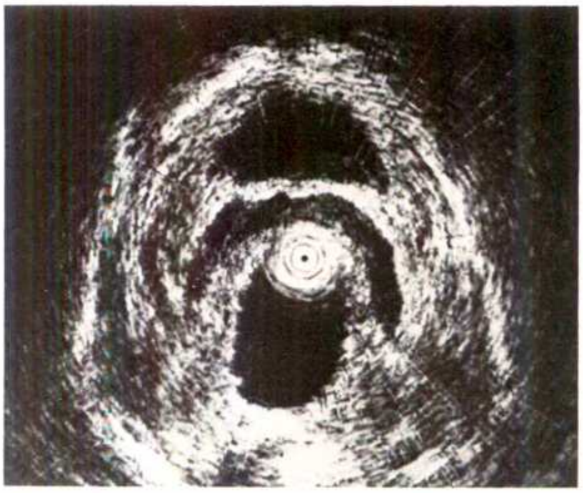

Fig. 2 Ultrasound scan showing base of bladder and seminal vesicles posteriorly.

The highest scans showed the base of the bladder, at which level the seminal vesicles appeared as symmetrically curved transonic regions behind it (Fig. 2).

Benign Hyperplasia In benign hyperplasia the capsule was also clearly represented but its shape was more rounded and spherical than in a normal gland. Again, there was an homogeneous echo pattern from the parenchyma of the gland (Fig. 3).

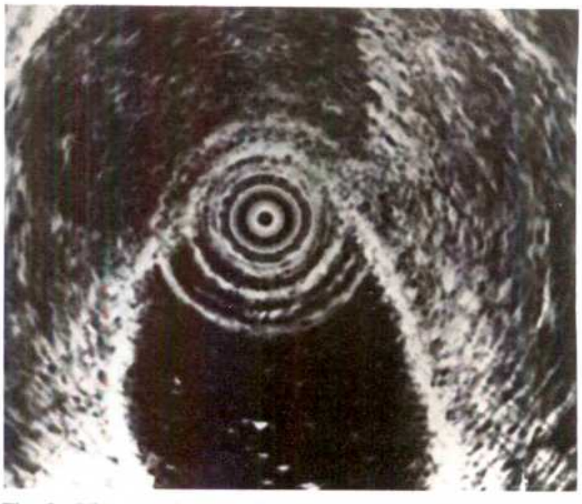

Fig. 3 Ultrasound scan of benign prostatic hyperplasia.

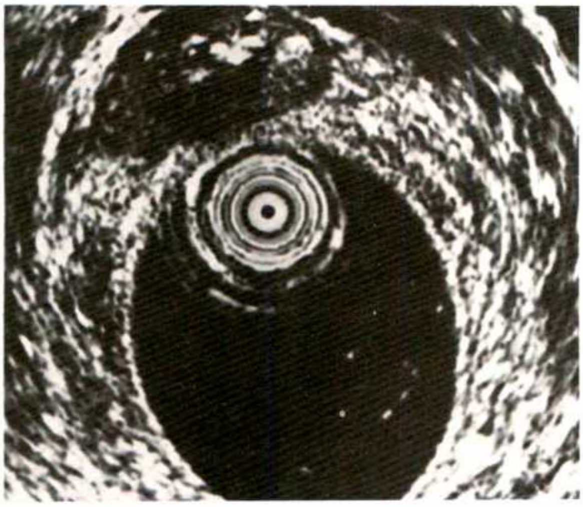

Fig. 4 Ultrasound scan of carcinoma of the prostate showing echodense regions within an intact capsule (Stage T2).

Prostatic Cancer Prostatic cancer was considered to be represented by echodense regions within the gland—provided that prostatic calcification was not visible on X-ray. Only when the capsule was seen to be intact at all levels of scanning was a carcinoma considered to be *confined* within the prostate (Fig. 4).

A break in the continuity of the capsule was considered to demonstrate locally invasive, *unconfined* disease (Fig. 5).

The Prostatic Capsule (Table 2)

The prostatic capsule was clearly definable in 58 out of the 60 subjects that were studied. Scans were not obtained from 2 patients, one because of technical breakdown of the equipment and the other because the tumour was too large to allow the probe to enter the rectum safely.

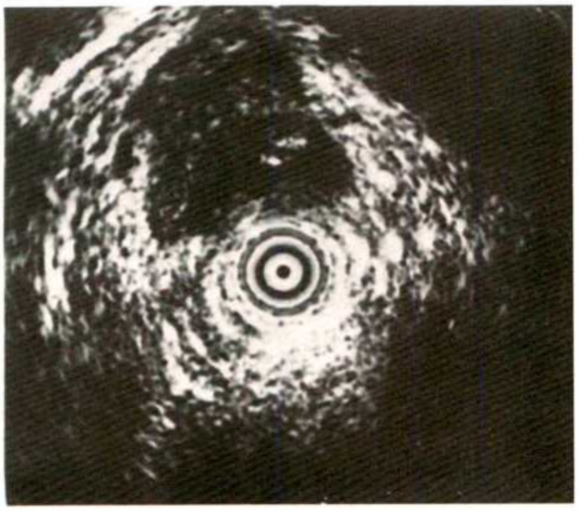

Fig. 5 Ultrasound scan of carcinoma of the prostate showing an anterior breach of the capsule. (Clinically, Stage T2; Ultrasonically, Stage T3.)

Table 2 Prostatic Capsules

Clinical diagnosis	*Clarity of definition*			*Not intact*
	Good	*Uncertain*	*Nil*	
Normal (7)	7	—	—	—
B.P.H. (11)	11	—	—	—
Ca P (35)	33	—	2	16
"Nodule" ± B.P.H. (7)	7	—	—	1
All cases (60)	58	—	2	17

The only patients in whom the capsule was *not intact* were those with proven cancer and these included one man with a prostatic nodule that was proved to be malignant by needle biopsy.

The Seminal Vesicles (Table 3)

The seminal vesicles were seen clearly in scans of only 39 out of the 60 men studied. They were not visualised in 20 men, 9 of whom had invasive prostatic cancer, but it was not possible to establish by ultrasound whether the vesicles in these patients were diseased or merely empty. However, it is likely that when the vesicles were seen on ultrasound scan they were normal.

Ultrasonic Detection of Prostatic Cancer (Table 4)

Forty patients were reported to have ultrasonic features that suggested the presence of prostatic cancer. This was not confirmed histologically by needle biopsy of the 2 suspects with clinically benign disease, but the ultrasound diagnosis was

Table 3 Seminal Vesicles

Clinical diagnosis	*Clearly seen*	*Not seen*	
		Bilat.	*Unilat.*
Normal (7)	5	1	1
B.P.H. (11)	7	3	1
Ca P (35)	22	*10 (1)	2
"Nodule" ± B.P.H. (7)	5	—	† 2
All cases (60)	39	14 (1)	6

* 9 with "unconfined" Ca P
† 1 with "confined" Ca P

Table 4 Reliability of Ultrasound Report in the Detection of Ca P

Ultrasonic features of Ca reported	*No.*	*Histological diagnosis of Ca P*
In B.P.H. group	2	0
In Ca P group	32	33
In "nodule" ± B.P.H. group	6	3

correct for 32 of the 33 men with proven prostatic cancer. Six men with a prostatic nodule of uncertain character also had ultrasonic features suggesting carcinoma and of these 3 were proved by needle biopsy to have cancer.

Ultrasonic Staging of Prostatic Cancer (Table 5)

Clinical staging by rectal palpation of 33 patients with prostatic cancer was compared with staging made by ultrasonic scan. Staging by these methods agreed for 18, was uncertain in 2 and disagreed for 13 cases. These patients consisted of 18 men in whom the cancer was considered to have been still confined within the capsule of the prostate on rectal assessment, 11 in whom it had apparently broken through, and 4 with controlled, treated disease in whom the prostate did not feel abnormal. Ultrasonically, 9 of the men with clinically "confined" disease had intact prostatic capsules, but 7 others showed clear perforations of the capsule; in 6 of these, perforation was *anterior*. Of the patients with clinically "unconfined" invasive disease, the ultrasound scan showed specific posterior or lateral perforations of the capsule in 6 patients and there was general disorganisation of the capsule in the remaining 3. However, in 2 cases ultrasound scan showed that the tumour had been overstaged clinically, for the capsule was intact.

It was also interesting that 4 men with controlled, treated prostatic cancer whose prostates did not feel abnormal had definite ultrasonic evidence of cancer within the prostate and evidence of capsular perforation in one case.

Table 5 Agreement Between Ultrasound and Clinical Staging

Clinical diagnosis		*Yes*	*Uncertain*	*No*
Ca P	*(33)*	*18*	*2*	*13*
"Confined" Ca P	(18)	9	2	7
"Unconfined" Ca P	(11)	9	0	2
"Controlled" Ca P with "normal" gland	(4)	0	0	4

Discussion

In our experience, transrectal prostatic ultrasonography with the Aloka chair-mounted probe has been a safe and easy procedure, for there have been no significant complications from 69 examinations. It has been acceptable to 66 out of 69 patients, many of whom were out-patients, and has been repeated without complaint on 6 men. In 58 of 60 men, the prostatic capsule was clearly detectable but the seminal vesicles were seen only in about two-thirds of examinations. Capsular perforation was noted only in patients with established and proven prostatic cancer.

Clinically, it was encouraging that ultrasound scanning identified 32 out of 33 men with proven prostatic cancer, and it was particularly useful in identifying those with suspicious lesions that should be biopsied.

Perhaps the most clear-cut application of ultrasound scanning in this study related to staging of prostatic cancer. It was reassuring to find that clinical and ultrasound evaluation agreed when the cancer had perforated the prostatic capsule posteriorly or laterally, but this is to be expected for this is the palpable part of the gland. It was disturbing to find, on the other hand, that nearly half of the patients with clinically localised disease had invasive cancer anteriorly, a site which can not be felt by the clinician's finger (Fig. 5). Clearly, the strength of ultrasound scanning of the prostate is its ability to look at the clinician's blind spot, which is the front of the prostatic capsule, and in our experience it has added an extra dimension to the clinical evaluation of prostatic cancer.

We conclude from this preliminary study that transrectal ultrasonography of the prostate with the Aloka probe is a safe and useful investigation, that combination with the Searle PhoSonic "B" Mode Scanner has produced scans of a high technical quality, and that this investigation is applicable within the clinical field to the early diagnosis and staging of prostatic cancer.

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Urinary Hydroxyproline Excretion in Carcinoma of the Prostate. A Comparison of 4 Different Modes of Assessment and its Role as a Marker

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Summary—Urinary hydroxyproline (HP) excretion has been estimated without prior dietary restriction in 33 patients with carcinoma of the prostate and expressed as either 24-h HP output or as the hydroxyproline/creatinine (HP/Cr) ratio in a 24-h urine sample, an early morning urine sample or a spot urine sample.

The early morning urine hydroxyproline/creatinine ratio (EMU HP/Cr) appears to be the most accurate and avoids the disadvantages of formal dietary restriction and prolonged urine collection. The rest is useful in monitoring the response to treatment of a patient with bony metastatic disease and relapse of a patient when his tumour ceases to be hormone sensitive. Furthermore, changes in EMU HP/Cr occur earlier than changes in other clinical or investigative variables, giving the test predictive value.

The amino acid hydroxyproline (HP) occurs almost exclusively in collagen, where it accounts for 13% of the total amino acids. Two-thirds of body collagen is in bone, where it forms 90% of bone matrix or 30% of bone weight (Neuman and Logan, 1950). Degradation of collagen releases HP back into the circulation, about 10% of which is excreted in the urine, the remainder being further metabolised to carbon dioxide and urea (Cuschieri, 1973). Total urinary HP is 5 to 10% in the free form and 90 to 95% peptide bound (Prockop and Kivirikko, 1967). In a variety of conditions in which bone formation or destruction are excessive, including metastatic bone disease, an increase in urinary HP excretion is observed (Hosley *et al.*, 1966; Bonnadonna *et al.*, 1966; Prockop and Kivirikko, 1967). In metastatic breast cancer total urinary HP has been reported to be more sensitive as an index of bone destruction, with disease progression or bone healing in response to treatment, than X-rays or bone scanning (Cuschieri, 1973; Powles *et al.*, 1975; 1976; Gielen *et al.*, 1976). Total urinary HP has also been shown to be more reliable than other markers of the presence and activity of bone metastases in carcinoma of the prostate (Bishop and Fellows, 1977).

Most investigators have studied total HP excretion (Hosley *et al.*, 1966; Prockop and Kivirikko, 1967; Bishop and Fellows, 1977) or the ratio of hydroxyproline to creatinine (Guzzo *et al.*, 1969; Powles *et al.*, 1975) in an accurately collected 24-h urine sample and this has obvious drawbacks. Furthermore, it is customary to impose a low gelatin diet for 24 h or more before the urine collection is begun, as dietary gelatin can increase urinary HP output (Prockop and Sjoerdsma, 1961). This is also a disadvantage and perhaps explains why the test has not gained wider acceptance.

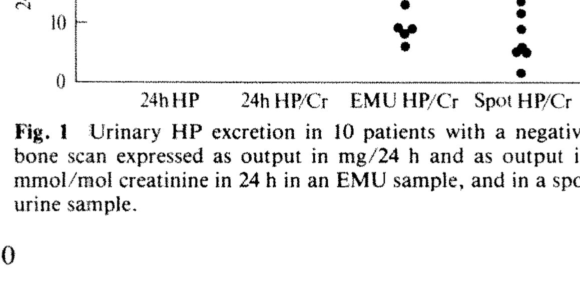

Fig. 1 Urinary HP excretion in 10 patients with a negative bone scan expressed as output in mg/24 h and as output in mmol/mol creatinine in 24 h in an EMU sample, and in a spot urine sample.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

The present study was designed to assess the value of hydroxyproline/creatinine ratios in an early morning urine sample *i.e.* after an overnight fast, and in a spot urine sample as compared with the more usual total urinary HP or HP/Cr ratio in a 24-h urine sample, but again without dietary restriction.

In addition, the study assessed the value of this measurement as an index of remission or relapse on treatment.

Patients and Methods

Thirty-three patients (aged 56-77) with histologically proven carcinoma of the prostate were studied. Sixteen patients were new cases, 10 of whom had skeletal metastases on bone scanning (99m Tc MDP-Radiochemical, Amersham) with X-rays when the scan was equivocal; 17 patients were being followed up on treatment. Of these 17 patients, 13 had positive bone scans. Hormonal treatment in M1 disease was either stilboestrol 1 mg tds or bilateral orchiectomy with radiotherapy to the prostate in M0 disease. Patients with disease progression despite hormonal treatment (9 cases) had either palliative radiotherapy or systemic cytotoxic chemotherapy subsequently.

On preliminary assessment of all patients whilst in hospital, 24-h urine samples were collected on 2 consecutive days with aliquots taken from early morning urine (before breakfast), and from one sample passed at some time during the day. Subsequent follow-up was on an out-patient basis with the patients attending a urological tumour clinic held in the morning. The patients gave a urine specimen on arrival, having had no breakfast.

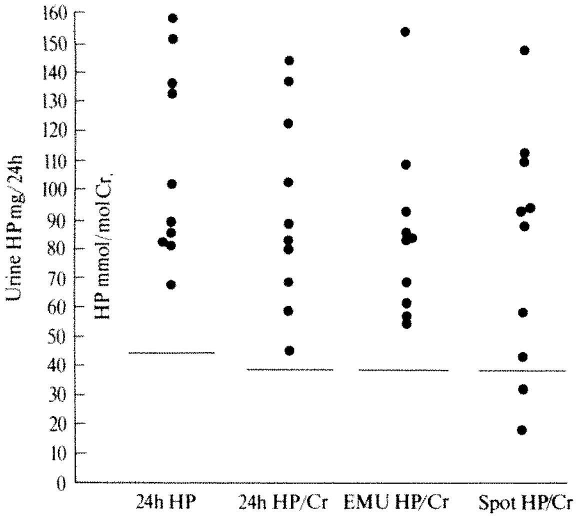

Fig. 2 Urinary HP excretion in 10 untreated patients with a positive bone scan expressed as output in mg/24 h and as output in mmol/mol creatinine in 24 h, in an EMU sample and in a spot urine sample.

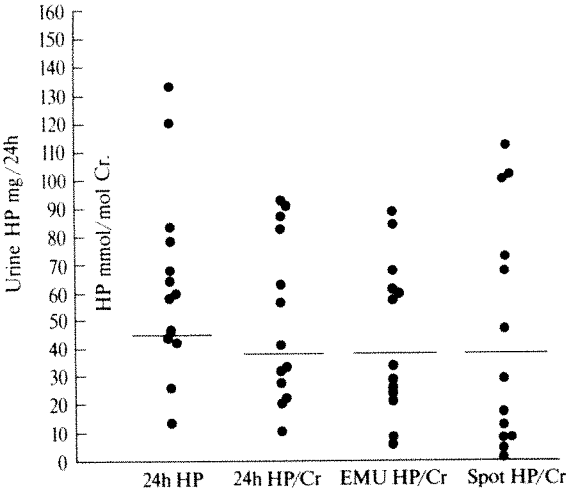

Fig. 3 Urinary HP excretion in 13 treated patients with a positive bone scan expressed as output in mg/24 h and as output in mmol/mol creatinine in 24 h, in an EMU sample and in a spot urine sample.

Creatinine levels were measured by a Vickers Autoanalyser and hydroxyproline levels by a colorimetric reaction with Ehrlich's reagent after overnight hydrolysis and subsequent oxidation (Prockop and Udenfriend, 1960), the free and peptide-bound fractions being measured together as total hydroxyproline.

Results

Urinary HP Excretion (Figs. 1, 2 and 3)

The normal range was 15 to 45 mg/24 h for our laboratory. Two patients of the 10 with a negative bone scan had levels above the upper limit of normal; neither showed subsequent disease progression and both had normal EMU HP/Cr ratios. All untreated patients with a positive bone scan had levels above the normal range. Patients with hormonal treatment and positive bone scans showed values both within and above the normal range.

Urinary HP/Cr Ratio (Figs. 1, 2 and 3)

The normal level was less than 39 mmol/mol creatinine. As compared with the bone scan in scan-negative and untreated scan-positive patients,

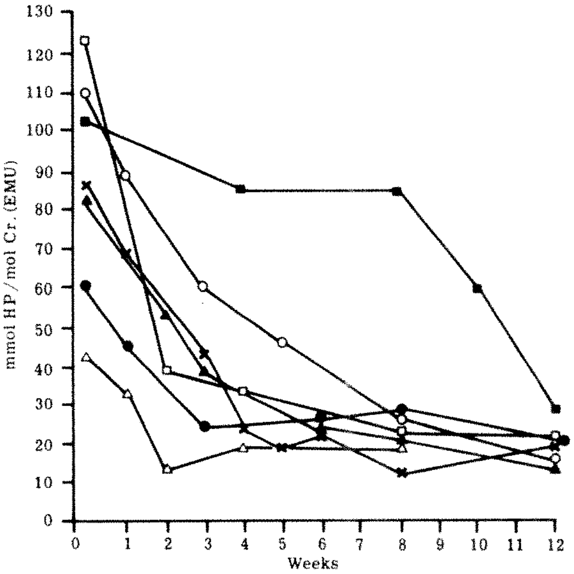

Fig. 4 EMU hydroxyproline/creatinine ratios in 5 patients showing response to treatment.

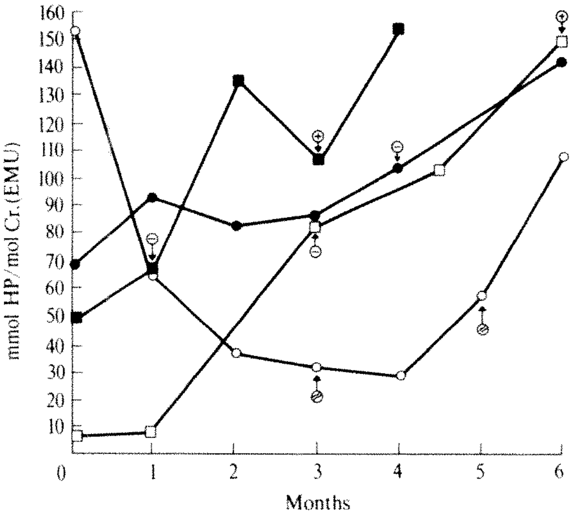

Fig. 5 EMU hydroxyproline/creatinine in 4 patients showing disease progression.

only the EMU HP/Cr levels showed complete correlation, with false positives in the 24-h HP/Cr levels and false positives and negatives in the spot HP/Cr levels.

In the treated group of patients there were again levels both within and above the normal range of all 3 ratios. All treated patients with an elevated EMU HP/Cr ratio showed disease progression at that time or subsequently by other clinical or investigative measurements.

EMU HP/Cr Ratio During Follow-up

The 10 patients with skeletal metastases at first presentation all responded to hormonal treatment by clinical and laboratory criteria. The EMU HP/Cr ratio fell to normal levels usually within 2 to 4 weeks of starting treatment (range 1-12 weeks). Figure 4 illustrates 7 such patients. Improvement in the bone scan usually took 3 to 4 months.

Those patients without skeletal metastases (10 patients) and those treated patients with positive bone scans without evidence of progressive disease (6 patients) consistently showed EMU HP/Cr ratios within the normal range.

Patients who showed disease progression on follow-up demonstrated increased levels of EMU HP/Cr ratio 2 to 4 months, on average, before any other detectable change. Figure 5 shows 4 such patients, one of whom (G.C.) initially improved on treatment and subsequently escaped from hormonal control, whose condition had deteriorated with a rising EMU HP/Cr ratio while his bone scan still showed improvement.

Discussion

There have been several studies attesting to the value of elevated urinary HP levels as a sensitive indicator of bone deposits in malignant disease, including carcinoma of the prostate (Bonnadonna *et al.*, 1966; Hosley *et al.*, 1966). Bishop and Fellows (1977) showed the reliability of this test as compared with bone scanning and that normal levels in patients with a positive bone scan on hormonal treatment correlated with symptomatic. remission. The results presented in this study confirm these findings.

Urinary HP levels reflect bone collagen turnover but dietary factors, especially gelatin, can also increase urinary HP. The main foods involved

Table 1 Foods That May Cause Increased Urinary HP

Gelatin
Meat and meat skins. Canned meat
Fish. Canned fish
Ice cream
Sweets and chocolate
Synthetic cream
Jelly
Pie-fillings
Milk and milk products
Cake decorations

Table 2 Diseases That May Cause Increased Urinary HP

Paget's disease of bone
Malignant disease with bony metastases
Hyperparathyroid bone disease
Thyrotoxicosis
Acromegaly
Rickets
Fibrous dysplasia of bone
Collagen diseases
Hypertrophic pulmonary osteoarthropathy
Pregnancy
Psoriasis
Thermal burns
Kleinfelter's disease
Turner's syndrome
Sarcoidosis
Malabsorption with secondary osteomalacia
Marfan's syndrome
Hurler's syndrome

(Table 1) are usually restricted for 1 to 4 days before urinary HP levels are estimated.

It has been shown, however (Powles *et al.*, 1976) that normal overnight fasting is sufficient to produce reliable urinary HP levels, with less day-to-day variation than in 24-h studies, presumably because the effect of dietary ingestion of gelatin on urinary HP excretion is short-lived. Our results support this.

Although other conditions may cause increased HP excretion (Table 2), these can usually be easily excluded in an individual case and lack of specificity may be argued against other investigations, including bone scanning. The EMU HP/Cr ratio is cheap, reliable, does not require the inconveniences and possible inaccuracies of prolonged urine collection or dietary restriction, and can be used in hospitals without the facilities for bone scanning. This is not to say that HP excretion levels and bone scans are comparable investigations in metastatic bone disease, as our results to date show no evidence that raised urinary HP levels occur before a bone scan, previously negative, becomes positive, although increased HP excretion has been shown to occur before a positive bone scan becomes more or less positive in relapse or remission respectively. HP excretion reflects only collagen breakdown in bone, whereas accumulation of 99m Tc isotopes in bone reflects osteoblastic activity in forming and mineralising new collagen (Lentle *et al.*, 1976). Furthermore, a bone scan gives localisation of bony deposits. In addition, the extent of bony metastases can be shown on a scan which does not in our experience relate to the level of urinary HP excretion. Thus the 2 tests are complimentary.

Urinary HP excretion may, however, reflect changes in the activity of bony deposits more accurately than a bone scan, as our results have shown changes in HP excretion occurring a considerable period before changes in the bone scan and, in patients on treatment with a positive bone scan, these results show that the EMU HP/Cr ratio can distinguish between skeletal and hepatic deposits as a cause for an elevated serum alkaline phosphatase (Hosley *et al.*, 1966).

Katz and Kappas (1968) have shown that oestrogens (and androgens) in pharmacological amounts substantially reduce urinary HP levels, the mechanism of which is unclear, in men and women without malignant disease. The results of this study show that a return of the EMU HP/Cr ratio to normal on treatment in men with metastatic carcinoma of the prostate involving bone is always associated with symptomatic remission and an improvement in other measurements.

The results presented here indicate also the early predictive value in assessing a patient's response to, or escape from, hormonal control (Powles *et al.*, 1975). It is also most helpful, in our experience, in being the earliest objective sign, in hormone-escaped patients receiving systemic cytotoxic chemotherapy, of response to treatment, enabling a decision at a relatively early stage as to the advisability of continuing a form of treatment with so many potential problems.

Acknowledgements

I am grateful to Mr C. H. Kinder, Mr J. F. Flannery and Mr M. R. L. Joyce for allowing me to study patients under their care and for their encouragement and advice during this study, and to Miss D. A. McGlynn for her help in preparing the typescript.

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Transitional Cell Carcinoma of the Prostate

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Summary—Thirty-three cases of transitional cell carcinoma involving the prostate gland are reviewed. Four different types of involvement are described. The mortality of 66% was largely confined to those with primary prostatic transitional cell carcinoma and those in whom there was direct invasion of the prostate by a bladder tumour. The relationship of some of these lesions to urothelial carcinoma *in situ* is discussed.

Although primary transitional cell carcinoma of the prostate is well recognised (Greene *et al.*, 1976), as are similar lesions associated with bladder tumours (Johnson *et al.*, 1972; Schellhammer *et al.*, 1977), the finding of a transitional cell tumour in an organ more commonly the site of adenocarcinoma often comes as a surprise to the clinician, who may be unsure how best to manage the patient.

Interpretation of the histopathology of lesions in this region can present difficulties for the pathologist. This paper reviews a series of patients with various types of involvement of the prostate by transitional cell carcinoma.

Patients

Thirty-three patients with transitional cell carcinoma of the prostate, seen in the Urological Units of Bristol and Exeter over a 6-year period from 1973, are considered. Their case records have been reviewed retrospectively and the histological slides re-examined

Results

The series has been divided into 4 groups of patients (Table 1):

Table 1 Involvement of the Prostate Gland by Transitional Cell Carcinoma

	No. of patients
Group 1. Invasion of the prostate by a bladder tumour	7
Group 2. Previous bladder tumour; Recurrence in prostate	6
Group 3. Generalised urothelial carcinoma *in situ*	5
Group 4. Apparent primary prostatic tumour	15
Total	33

Group 1. Invasion of the Prostate by a Bladder Tumour (7 patients)

These are patients in whom there was a tumour, seen at cystoscopy to be arising in the bladder, with histological evidence of invasion of the prostate. Where such invasion could not be confirmed histologically the case was excluded from the series. Two had huge malignant masses replacing the prostate and occupying most of the bladder. The remaining tumours were more localised. One patient had previously had tumours elsewhere in the bladder. The survival times given in Table 2 are from the date of diagnosis of prostatic invasion.

Table 2 Invasion of the Prostate by a Bladder Tumour (Group 1)

Number of patients		7
Ages	58-75	
Deaths		7
Survival	2/52-19/12	

Group 2. Previous Bladder Tumour; Recurrence in Prostate (6 patients)

These patients had a history of discrete bladder tumours (Table 3). One, in whom the bladder tumours had been of low grade, had a less well differentiated average grade prostatic recurrence;

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Table 3 Recurrence in Prostate: Previous Bladder Tumour (Group 2)

Number of patients	6
Ages	61-73
Histological grade	
High	1
Average	1
Low	4
(Change in grade	1)
Length of previous history of TCC	2-26 years
Death	1

in the remainder the original grade was reflected by the lesion in the prostate. Some of the prostatic lesions proved difficult to eradicate, requiring repeated resections and in one case radiotherapy. Otherwise the clinical course was that to be expected for the grade of tumour. The only patient to die had a poorly differentiated high grade lesion.

Group 3. Generalised Urothelial Carcinoma in situ (5 patients)

Two patients with carcinoma *in situ* (Skinner *et al.*, 1974) without macroscopic tumours first had the presence of transitional cell carcinoma diagnosed from prostatic curettings. One has had a total cystectomy. In addition, 3 patients who appeared to fall into the previous group (*i.e.* recurrent tumours) were found, when their histology was re-examined, to have carcinoma *in situ* in the areas intervening between the macroscopic lesions. Two patients have died.

Group 4. Apparent Primary Prostatic Tumours (15 patients)

These patients were usually assessed on clinical and endoscopic grounds as having a prostatic "carcinoma". Most presented with obstructive symptoms (Table 4). Although haematuria was common it was the main sign in only 2 patients. Franzen needle aspiration had been performed in 6 patients but the only patient in whom malignant *transitional* cells were clearly identified cytologically had already had the diagnosis established by histology. In the others, although "malignant" cells were identified, in 2 they were described as "adenocarcinoma" and the remainder were not defined further. Serum acid phosphatase measurements were available for 10 patients; 9 were within the normal range. In most cases the true diagnosis was made only from the histology, by which time some patients had already been prescribed stilboestrol or (where a "positive" cytology had been reported pre-operatively) subjected to orchiectomy.

Table 4 Primary Prostatic Tumours: Presentation (Group 4)

Number of patients	15
Age	mean 71 range 57-84
Symptoms	
Prostatism	12
(retention	5)
Haematuria	7
Pain	4
Metastases	1
Palpation of prostate	
Benign	1
Carcinoma	11
Abnormal	2
Endoscopic assessment	
Prostatic carcinoma	13
Not specified	2

These patients were treated by various methods (Table 5). Hormone treatment was used, even when the diagnosis was known, in an attempt to control rapidly progressive disease. Although initially there was a subjective impression of improvement in a few patients after radiotherapy, the various treatments had little effect on the clinical course of the disease (Table 5). The 2 patients whose ultimate fate could not be determined either from the hospital records or their general practitioners, had advanced tumour when last seen and it must be assumed that they have died.

Pathology of Apparent Primary Prostatic Tumours

On careful reassessment of the histology of these lesions, 3 patterns were found:

1. Tumour could be clearly identified in the

Table 5 Primary Prostatic Tumours: Treatment and Outcome

Treatment	
Transurethral resection	15
Oestrogens	5
Orchiectomy	7
Radiotherapy	10
Cyclophosphamide	1
Palliative Diversion	2
Outcome	
Dead (Survival 2/12-2 years)	11
Alive (at 1 year, 2 years)	2
Unknown	2
Surviving at 1 year	7

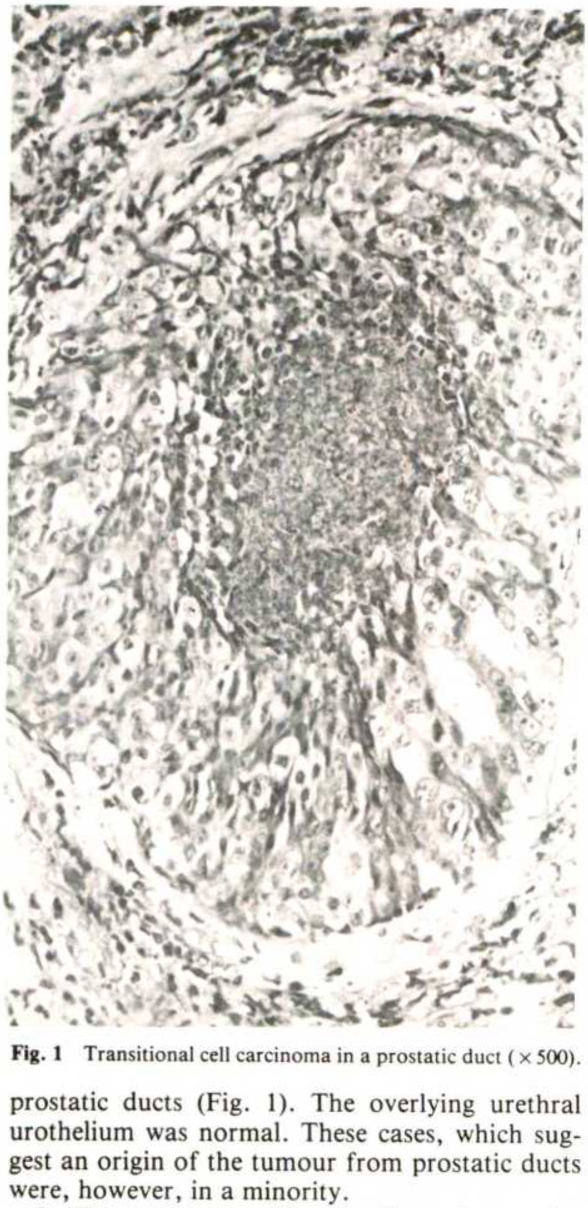

Fig. 1 Transitional cell carcinoma in a prostatic duct (× 500).

prostatic ducts (Fig. 1). The overlying urethral urothelium was normal. These cases, which suggest an origin of the tumour from prostatic ducts were, however, in a minority.

2. There was transitional cell carcinoma invading the prostate, but the site of origin could not be determined with certainty from the material available to the pathologist, usually because of the advanced nature of the lesion.

3. In a few cases, in addition to invasive carcinoma in the prostate, there was clear evidence of carcinoma *in situ* in the fragments of urethral uretholium among the curettings (Fig. 2).

Discussion

Overall, only one-third of this series of patients has survived. The deaths were mainly among those patients in Groups 1 and 4. The high mortality associated with invasion of the prostate by a bladder tumour (Whitmore and Marshall, 1962) and the poor prognosis of primary prostatic transitional cell carcinoma are well documented (Greene *et al.*, 1976).

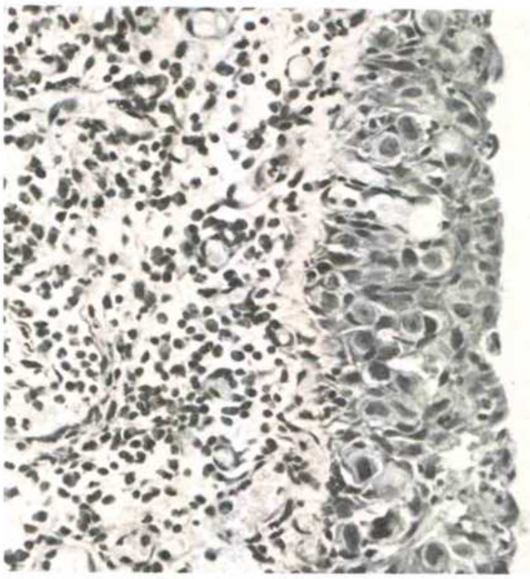

Fig. 2 Carcinoma *in situ* of the urethral urothelium (× 500).

The failure of the therapeutic measures used in the patients with primary prostatic tumours described here is confirmed in previous reports. The few long term survivors that have been described have usually been treated by radical prostatectomy or total cystoprostatectomy. In view of the poor results of other methods of treatment an aggressive surgical approach might be considered in suitable patients with primary prostatic transitional cell carcinoma. In contrast, invasion of the prostate by a *bladder* tumour has been stated as a contraindication to cystectomy, which seems not to improve survival in these circumstances (Whitmore and Marshall, 1962).

The difficulty in diagnosing a prostatic transitional cell carcinoma before histology is available emphasises the importance of confirming the diagnosis before treating carcinoma of the prostate by hormone manipulation. Since it would appear that cytology may not be a reliable method of distinguishing between these 2 types of carcinoma, transitional cell carcinoma should be considered when hormone therapy instituted as a result of a "positive" Franzen aspirate alone does not produce a response.

Primary transitional cell carcinoma of the prostate is now a well recognised condition (Greene *et al.*, 1976) and usually is accepted as arising in the prostatic ducts (Ende *et al.*, 1963). However, when the tumour is advanced, the pathologist studying material attained with the resectoscope may be in some difficulty. If areas of prostatic intraduct carcinoma can be identified (Fig. 1), the lesion can be identified as a primary prostatic carcinoma with some confidence but, in their absence, the origin of the tumour can be determined only in consultation with the clinician. Even then, the possibility of invasion by a tumour originating in the urothelium of the bladder neck cannot be discounted and may account for some of our apparent "primary" tumours.

It has been proposed that primary prostatic transitional cell carcinoma is an entity distinct from other urothelial tumours (Ende *et al.*, 1963). This may be true in many cases, but the question of prostatic involvement in the generalised carcinoma *in situ* has also to be considered. Five patients could clearly be distinguished as a separate group (Group 3, Table 1). However, there were 2 patients from Group 4 in whom abnormalities of the bladder mucosa were described at cystoscopy, and in 1 of the 2 who underwent urinary diversion malignant cells were identified in a biopsy of the ureter. It comes as no surprise, therefore, to find that some of those patients apparently with primary prostatic tumours show changes of carcinoma *in situ* in the urethral urothelium (Fig. 2). This is a tissue which can usually be identified in resected prostatic tissue but is easily overlooked. Such tumours may be different from prostatic duct carcinoma; alternatively the intraduct change may be part of the same process.

Once the possibility of carcinoma *in situ* has been considered, confirmation would require bladder biopsies and we feel that the condition of the bladder mucosa should always be thought of in these patients. The distinction becomes important in planning any radical surgery. It might also account for some of the poor results from radiotherapy, if this were directed at the prostate alone.

This series of patients confirms that primary prostatic transitional cell carcinoma carries a very poor prognosis, as do bladder tumours that invade the prostate. Hormonal therapy and radiotherapy have little to offer these patients and perhaps radical surgery should be considered more often. Although the development of primary prostatic tumours in the prostatic ducts could be confirmed in some cases, the pathologist is often unable to determine the origin of the tumour. These tumours may not always be distinct entities since some of the cases described here had definite carcinoma *in situ* of the urothelium, and if this condition were sought specifically, it might be found more commonly in these patients.

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The Role of Selective Internal Urethrotomy in the Management of Urethral Stricture: a Multi-Centre Evaluation

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Summary—The advent of selective internal urethrotomy under direct vision has enabled precision endoscopic surgery to be undertaken on a wide range of urethral strictures. A multi-centre survey of 197 cases involving 322 urethrotomy procedures from 5 urological departments in England is reported. The overall results after a follow-up of up to 4 years suggest that there is no indication for further procedures currently existing in 160 (81%) of those cases subjected to selective internal urethrotomy. The additional injection of triamcinalone acetate into the strictured area prior to urethrotomy is recommended in resistant cases.

The procedure of selective internal urethrotomy is, in our opinion, the best primary method for the treatment of urethral stricture, and it is hoped this will reduce the indications for anastomotic or substitution urethroplasty.

The treatment of strictures of the urethra is one of the oldest problems facing the urological surgeon, and attempts to enlarge a stricture by internal urethrotomy have been made for at least 400 years. The names of Paré (1560), Physick (1795), Amussat and Reybard (1818), Civiale (1844), Maisonneuve (1853) and Otis (1872) are all associated with blind urethrotomy and their work has been well reviewed by Murphy (1972). The last 25 years have seen a resurgence and refinement of these traditional methods using either the Otis urethrotome alone (Katz and Waterhouse, 1971; Wise *et al.*, 1972; Carlton *et al.*, 1974), or observing the effects before and after Otis urethrotomy (Helmstein, 1964) or as now, operating in a precise manner under direct vision using the recently developed optical urethrotome (Keitzer *et al.*, 1961; Sachse, 1974, 1977; Lipsky and Hubmer, 1977; Kirchheim *et al.*, 1978; Matouschek, 1978, Smith *et al.*, 1978; Kinder and Rous, 1979).

The early British experience using the Sachse optical urethrotome has already been the subject of a communication by one of the authors (Smith *et al.*, 1978) and this paper records the overall experience of 5 English centres (Bath, Bristol, Norwich, Plymouth and Portsmouth) in selective internal urethrotomy. The objective throughout has been to keep the urethral trauma to a minimum and where necessary to try and modify the inevitable ensuing inflammatory response and prevent cicatricial scarring.

The use of direct vision urethrotomy will be considerable, if long-term results confirm a stable stricture, relieving bladder outflow obstructive symptoms and reducing the indications for anastomotic or substitution urethroplasty.

Method

Pre-operative evaluation of the patients has included excretion urography, ascending urethrography, measurement of urinary flow rate and urine culture. The operative procedures have been undertaken under general, regional or local anaesthesia. In all cases, the procedure as suggested by Sachse (1974) has been adopted, using the Storz urethrotome with 0° (direct vision) telescope and the full range of urethrotome knives.

The operative procedure has been further modified in 2 centres. In Plymouth Depo-medrone has

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Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 1 Source of Cases Evaluated

	No. of patients	*Duration of study (months)*
Bath	51	48
Bristol	12	18
Norwich	82	30
Plymouth	41	18
Portsmouth	11	26
	197	

been injected into the site of the urethrotomy and the patient maintained on oral prednisolone for 2 weeks post-operatively, whilst in Norwich triamcinolone acetate has been injected into the strictured area before incision *only* in those cases which have failed to respond to 2 previous urethrotomies. Following the visualisation of the stricture face, the strictured channel has invariably been cannulated using a 3 FG calibrated retrograde ureteric catheter to avoid creating a false passage with the urethrotomy knife. Incision into the strictured urethra, with a *sharp* blade, has been confined to the 12 o'clock position with the cutting blade extended and moving the whole instrument *en bloc* in an upward and outward direction. It is important that the incision extends not only through the full thickness of the maximally strictured segment but also both proximally and distally into macroscopically normal urethral tissue. Bleeding points have occasionally been diathermised, exchanging the knife blade for a standard diathermy electrode.

Following urethrotomy, an 18 FG self-retaining catheter on an introducer has been inserted into the bladder and left *in situ* for 1 to 7 days. Antibiotic cover was not used unless there was a history of previous proven urinary infection, the urine appeared infected at the time of operation, or the stricture followed a urethroplasty. Post-operative hydraulic dilatation of the urethra (Marshall *et al.*, 1971) has been advised at 2 centres (Norwich and Portsmouth) to try and minimise bridging across the healing area within the urethra.

Table 2 Stricture Aetiology

			No. of patients
Congenital			10 (5.1%)
Inflammatory			30 (15.2%)
Traumatic:			
1. Ruptured urethra		15	120 (61.2%)
2. Instrumentation alone	19	105	
RPP/TVP	32		
TUR	54		
Post-urethroplasty			16 (8.1%)
Unknown			21 (10.4%)
Total			197

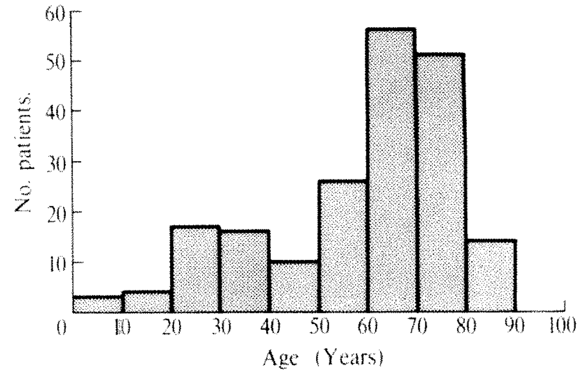

Fig. 1 Age distribution at first urethrotomy.

Patients and Results

Selective internal urethrotomy was performed on 197 patients involving 322 procedures with a follow-up of up to 4 years (Table 1). The age distribution of the patients prior to their first urethrotomy is shown in Figure 1 with 75% of the cases over the age of 50 years. The aetiology of the strictures is given in Table 2: 10 (5.1%) had a congenital basis, 30 (15.2%) were due to infective causes, 16 (8.1%) followed attempts at urethroplasty correction and 21 (10.4%) were of uncertain aetiology. A large proportion, however, were of traumatic origin (120 cases, 61.2%), and of these 105 (53.5%) were due to previous urethral manipulation. The site occupied by the stricture within the urethra (A) is shown in Table 3 together with the overall number of urethrotomies performed (B) at each particular site. The ratio B:A gives a true indication of the responsiveness of a stricture to urethrotomy.

An attempt has also been made to demonstrate, as precisely as possible, the stricture site within the bulbous urethra and this was done by 4 centres (Table 4). The majority of those cases occurring within the *mid* bulbous urethra were related to previous urethral trauma by either instruments or catheters.

The incidence of complications following selective internal urethrotomy has been 8.4%, the problems being of a transient rather than a long standing nature (Table 5). There have been no instances of impotence, incontinence or the

Table 3 Stricture Site Within the Urethra

	Navicular fossa	*Ant. (penile) urethra*	*Mixed ant. and bulbous urethra*	*Bulbous urethra*	*Membranous urethra*	*Bladder neck*
A. No. of cases per site	1	28	23	111	31	18
B. Overall no. of urethrotomies performed at each site	1	48	43	161	51	18
Ratio B:A	1.0	1.71	1.87	1.45	1.64	1.0

development of chordee in this series to date. The patients have been reviewed regularly at 3- to 4-monthly intervals, using out-patient evaluation, endoscopy and urinary flow rates. A flow rate of greater than 15 ml/s has been accepted as satisfactory evidence of a reasonable urethral calibre. Repeat urethrographic studies have not been done routinely as previous workers have not necessarily demonstrated a good correlation between the urethrogram and the actual extent of the diseased urethra (Lapides and Stone, 1968; Shaver *et al.*, 1975). The duration of follow-up in this series of patients as of May 1979 is given in Figure 2. The effectiveness of the treatment is indicated by the rate of discharge from further operative procedures of any type to either the out-patient department or to general practitioner follow-up (Table 6).

There has been no obvious benefit in relation to either patient numbers or stricture siting from the use of Depo-medrone when the rates of discharge of the patient from further procedures are compared with those of the other 4 centres. The use of triamcinolone in Norwich has been useful in modifying and preventing recurrent stricture formation in those patients who have not responded to 2 initial urethrotomy operations.

Discussion

The principle that lies behind selective internal urethrotomy is to minimise tissue trauma in zones where there is already excessive scar tissue formation. This is in great contrast to the repetitive and unvisualised trauma that takes place with frequent urethral dilation or "calibration". The results in this series to date would suggest that this operation (160 (81%) out of 197 cases already discharged from further operative procedures) has a wide application and should, as many authors have already suggested (Sachse, 1974; Matouschek, 1978; Kinder and Rous, 1979) be employed as the primary treatment of choice for urethral stricture. This technique may be applied to nearly all forms of urethral stricture, be they of short or long standing, and the truly impassable stricture which inevitably needs alternative therapy is in our opinion a rare event. It is worthwhile progressing beyond the second or third urethrotomy as there are 18 cases in this series which have subsequently responded with a stable scar.

This has been confirmed endoscopically, for it is appreciated that considerable narrowing of the urethra may occur, to about 10 FG, before significant reduction in urinary flow rate can be demonstrated with urodynamic studies.

Of those strictures within the bulbous urethra (Table 4) more than half were situated within the *middle third* of that structure and the aetiological

Table 4 Stricture Site Within the Bulbous Urethra*

	Bulbous urethra		
	Proximal	*Mid*	*Distal*
A. No. of cases per site	24	47	21
B. Overall no. of urethrotomies performed at each site	27	64	34
Ratio B:A	1.12	1.36	1.62

* Bath, Bristol, Norwich and Portsmouth only.

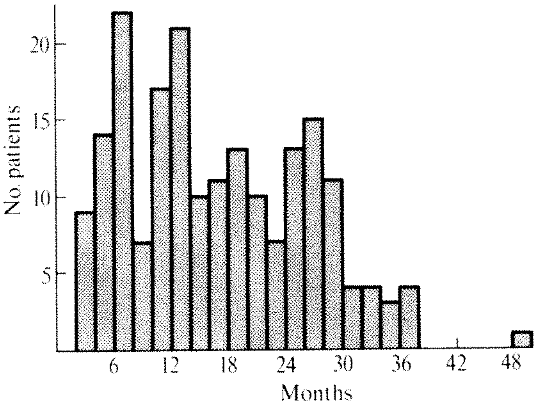

Fig. 2 Duration of follow-up up to May 1979.

Table 5 Complications Following Urethrotomy*

	No. of cases
Penile oedema	5
Haemorrhage (2 patients transfused)	10
Bacteriaemia/septicaemia	12
Epididymitis	0
Total	27 (8.4%)

* 322 procedures.

factor in most cases was that of previous manipulation, either by catheter or instrument within the urethra. Our evidence would suggest that this may well be the long-term consequence of pressure on the delicate submucosal vascular network within the bulbous urethra in particular and we would as a preventive measure also recommend preliminary internal urethrotomy before per-urethral surgery (Emmett *et al.*, 1963; Bailey and Shearer, 1979). Six cases have progressed from repetitive urethrotomy to either inlay urethroplasty (usually with extensive stricture disease) or less regular and easier out-patient urethral dilatation in the less fit case.

In an attempt to reduce stricture formation further, Sachse (1978) has recommended the self instillation of Terracortril-Gel into the urethra. Particularly in the resistant case, 2 of us (J.C.H. and C.G.C.G.) have been using intra-urethral steroid injections at the time of urethrotomy. Triamcinolone has previously been used to prevent hypertrophic scar, keloid and contracture development in plastic surgery (Ketchum *et al.*, 1966) and has recently found application in the treatment of vesical neck contracture (Farah *et al.*, 1979). Immediately preceding urethrotomy, 2 to 4 ml of 5 mg/ml triamcinolone acetonide have been injected into the strictured area circumferentially. It is felt that this is of undoubted benefit in the more resistant case and particularly where the stricture is of primary inflammatory origin and the pathology is still in the active phase.

Table 6 Patient Discharge Rate*

Urethrotomy number	*1*	*2*	*3*	*4*	*5*
No. of cases discharged from further procedures. (i.e. to O.P. or G.P. follow-up)	102	40	13	3	2

* Urinary flow rate greater than 15 ml/s.

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Endourethral Urethroplasty

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Summary—Following internal urethrotomy for treatment of strictures of the bulbous urethra, 11 patients had primary split skin grafts inlaid over the urethrotomy site. There were no operative complications and the results in 5 patients with a 9-month follow-up are good.

For many centuries dilatation remained not only the earliest but also the only form of treatment for urethral strictures. Urethrotomy was first performed in the eighteenth century and Otis in 1878 developed his urethrotome, one which is still in use in many parts of the world a century later. Internal urethrotomy under direct vision was first described by Helmstein (1964) and has largely superseded the blind technique. It rarely leads to a permanent cure (Blandy *et al.*, 1976). After internal urethrotomy the incision is left to heal by second intention. Scar tissue forms and usually contracts once the catheter is removed so that the stricture recurs. If a split skin graft is inserted and "takes" over the urethrotomy incision, scar tissue is less likely to form and the chance of recurrent stricture is reduced.

Many new forms of urethroplasty have been described during the last 20 years with a distinct improvement in the long-term results. We have performed a number of each type in order to evaluate them. In 1978, Pettersson *et al.* reported the technique of endourethral urethroplasty and we have used this method in 11 patients in order to assess its ease and efficacy.

Patients and Methods

During a 6-week period, 5 men were treated by endourethral urethroplasty for strictures of the bulbous urethra (Table). The duration of symptoms ranged from 2 to 45 years. More recently, a further 6 patients have since been treated. All had attended the dilatation clinic but either dilatations had become increasingly difficult or other complications had occurred. Urine cultures and a retrograde urethrogram were obtained preoperatively in all cases.

Operative Procedure

The operations were performed under general or spinal anaesthesia. Meatotomy and blind urethrotomy distal to the stricture were performed with an Otis urethrotome to enable a size 27 resectoscope sheath to pass easily. Urethroscopy was then performed using the Storz resectoscope and an incision was made using a Collin's knife under direct vision at 12 o'clock through the stricture into the periurethral fat (in case no. 3 the incision was made at 6 o'clock because of the previous perineal urethrostomy). Cystoscopy was then carried out. The distances between the bladder neck and the proximal and distal ends of the stricture were then measured using a ureteric catheter. These distances were then marked on a size 22 Silastic Foley catheter, the first distance of bladder neck to the proximal end of the stricture being measured from the balloon of the catheter. A thick split skin graft was then taken from the thigh. A thick graft was taken to lessen the retraction at the site of the incised stricture. This graft was then sutured on to the catheter with 4/0 chromic catgut with the epithelial surface towards the catheter. It was made 2 cm longer at each end than the measured stricture and was made tight around the catheter by suturing it to itself with continuous 4/0 chromic catgut. The catheter was then inserted into the urethra making sure that the graft suture line did not lie opposite to the urethrotomy site. The balloon was then inflated and the catheter withdrawn so that the balloon rested on the bladder neck. The bladder was filled with fluid until it became palpable and a suprapubic catheter was then inserted. Finally, the spigotted catheter was securely strapped to the abdominal wall and a firm well-

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Table Details of 5 Patients Treated by Endourethral Urethroplasty

	Patient	*Age*	*Aetiology*	*Symptoms*	*Duration*	*Previous treatment*
1	J.L.	66	G.C.	Very poor stream	30 years	Dilatations
2	L.F.	55	Post-catheterisation	Poor stream, acute retention	2 years	Urethrotomies × 2
3	L.C.	58	# pelvis	Difficulty in micturition, frequency and nocturia	45 years	Dilatations, perineal urethrostomy
4	V.J.	48	# pelvis	Poor flow	1 year	Dilatation failed
5	G.V.	21	Fall astride	Dysuria, urgency frequency and loin pain	2 years	Dilatations

padded compression dressing applied to the perineum.

Post-Operative Care

The dressing was retained for a week and the patient kept on strict bed rest. On the tenth day the donor area was exposed and on the seventeenth or eighteenth day the urethral catheter was removed and inspected for retained skin graft. In the first 2 cases the suprapubic catheter was retained for 4 weeks, but in the other 3 and with more recent patients it was spigotted once the urethral catheter was removed and, if micturition was satisfactorily re-established, it was removed. The patients were not given antibiotics unless an infection was present pre-operatively.

Follow-up Studies

Post-operative peak flow rates and urethroscopy were performed at 3 weeks, prior to discharge from hospital. All patients answered a questionnaire for subjective symptoms such as frequency, pain, stream, urgency, and sexual function at 6 and 9 months. Urethrograms were performed post-operatively and again at 6 and 9 months. Urethroscopy was repeated at similar times.

Results

Adequate follow-up was possible in all 5 patients up to 6 months but the last patient was unable to be present for the 9-months check. However, he is subjectively well and has agreed to return from Europe for the yearly appointment. None of the strictures has recurred, though one of the patients has developed symptoms of bladder neck stenosis over the last 3 months. Urethroscopy confirmed "take" of the graft over the urethrotomy site whilst the surplus was shed and passed *per urethram*. The size 20 urethroscope passed easily in all cases. Two patients subsequently developed urinary infections which required treatment with antibiotics.

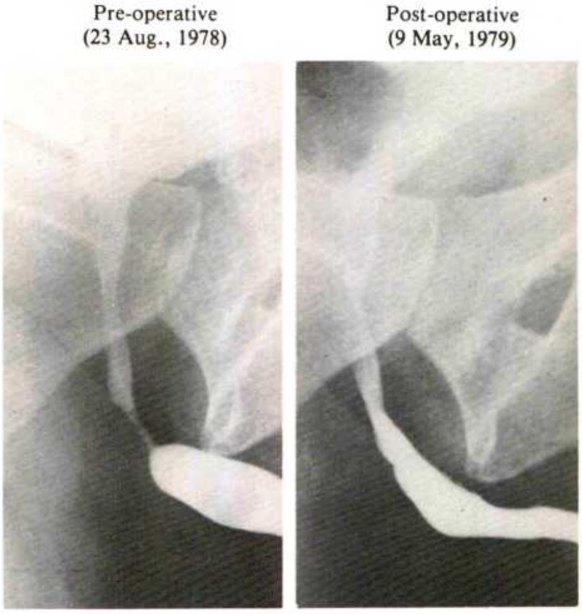

Fig. Pre-operative and post-operative urethrograms at 9 months. Case no. 1.

Urine flow rates, except for the man with the bladder neck problem, were within the normal range at 6 and 9 months. An average peak flow of 25 ml/s was obtained. All post-operative urethrograms showed increased urethral diameters at the site of the former stricture and no urethra measured less than 7 mm across at the stricture site (Fig.).

There were no operative complications in these 5 cases. In one case, in a further series, the balloon of the catheter burst. The suprapubic cystocatheter blocked in 2 patients on the tenth day but the bladder was drained via the urethral catheter without problem. One patient developed a transient bacteriaemia and the graft failed to take in another; this was the same patient in whom the balloon burst.

Discussion

The technique used was that of Pettersson *et al.*

(1978) who modified the original Nové-Josserand (1919) operation for repair of hypospadias. We measured the actual stricture length rather than measuring it on the urethrogram as we thought the latter technique open to error.

In comparison to other urethroplasties it is a simple, quick procedure. It seems a logical step after urethrotomy in order to prevent contraction from the scar tissue formation which often follows because of infection. Singh and Blandy (1976) showed that the post-traumatic inflammatory reaction in the rat urethra was much more severe when extravasation of urine occurred. Katz and Waterhouse (1971), Engel *et al.* (1972), Wise *et al.* (1972) and Smith *et al.* (1979), in order to reduce this inflammatory reaction after internal urethrotomy, all reported leaving indwelling urethral catheters for 3 weeks or even longer. Even the presence of a urethral catheter does not avoid secondary urethritis and infection at the urethrotomy site, and therefore we used a suprapubic catheter in an attempt to reduce urethral infection and promote primary healing.

As a skin graft will take only on incised tissues, and never on intact epithelium, the grafts were made longer than the strictures and we noted that the excess skin was shed when necrosed. For this reason split skin was used rather than full thickness grafts which would have taken much longer to necrose and be shed (Brannan *et al.*, 1976). Thick split skin grafts were deliberately taken to lessen the chances of contraction (McCormack, 1954).

Urine flow was measured during urodynamic assessment or by using a stop-watch and measuring container. Retrograde urethrograms were most impressive and confirmed that all urethrae were of a large diameter. Urethroscopy with photography enabled us to collect a record for future comparison.

The results in the first 5 patients were so encouraging that 6 more patients have been treated by this method this year. Although the follow-up period is short and the numbers too small for a comparative analysis, we feel the results in all but one of the 11 cases have been acceptable. There has been no recurrent stricture formation after a successful primary endourethral urethroplasty.

In conclusion, we feel that this type of urethroplasty is a safe, quick method of treating urethral strictures. All subjective and objective results, at the time of this preliminary report, are very satisfactory.

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A Technique for Selecting and Concentrating the Motile Sperm from Semen in Oligozoospermia

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Summary—Using an albumen-filled column, it was possible to separate highly motile sperm from autoagglutinated, dead and immotile sperm, as well as from other seminal debris. Motility was increased from a mean of 45.4 to 74.3% ($P<0.001$), although the sperm density fell from a mean of 28.2 million per ml to 9.7 million per ml ($P<0.001$). When these selected highly motile sperm were used for artificial insemination of husband's semen (AIH) in couples in whom conventional AIH had been repeatedly tried without success, 3 pregnancies were achieved in 18 women (16.7%).

In most cases when infertility is associated with poor sperm density or motility the cause is impossible to identify and no remedy can be found. Attempts at artificial insemination of husband's semen using this poor semen from the husband has met with little success (Dixon *et al.*, 1976; Speichinger and Mattox, 1976; Usherwood *et al.*, 1976; Usherwood, 1978). Ericsson *et al.* (1973) described a method whereby motile sperm could be separated from the rest of the semen. This method has been simplified and adapted by one of us (P.R.E.) for use in cases of male subfertility, and the purpose of this communication is to report our preliminary results.

Materials and Methods

Technique of Separation of Motile Sperm

Semen was obtained by masturbation into sterile plastic containers. If unduly viscous it was first washed and resuspended in phosphate-buffered saline (PBS). The semen was layered on top of 0.5 ml of Salt-poor Human Serum Albumen* in an insulin syringe (Fig. 1), using strict aseptic precautions. Several such "albumen-columns" were set up, according to the volume of semen available. Each syringe was kept upright at room temperature (20°C) for 1 h (Appell *et al.*, 1977).

The freely motile sperm were found to migrate down through the column of albumen and could be recovered by draining the albumen from the syringe. The resulting fluid was resuspended in sterile PBS, its sperm density and motility assessed, and then used either for intracervical or intrauterine insemination, in the method described by Usherwood *et al.* (1976).

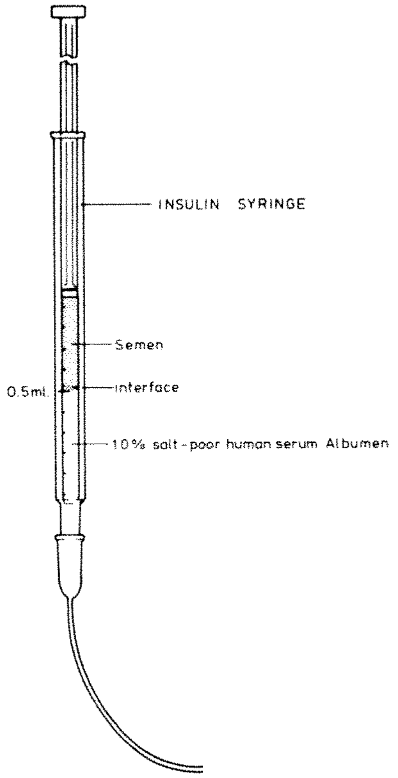

Fig. 1 Schematic drawing of albumen sperm separation column.

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* Cutter Laboratories, Berkeley, California.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 1 Initial Sperm Profiles

Sperm density × 10^6 per ml	*Motility %* < 30	 30-60	 > 60
≤10	○○	○○○	○
11-50	○○○○●	○○○	
≥51		●●	●●

● = agglutination.

AIH Using Separated Motile Sperm

This technique has been used in 18 couples, all of whom had been attending this infertility clinic for a minimum of 2 years. In each couple infertility was associated with low sperm density, low motility, or autoagglutination. Each couple had already undergone many cycles of conventional AIH using washed and unwashed sperm (Usherwood *et al.*, 1976). In all instances the wives had undergone complete investigations and were thought to be normal.

Motility and density were both poor in 13 cases; one couple had oligozoospermia but normal motility, 2 had normal sperm density but low motility and 2 had good counts and motility but very marked autoagglutination (Table 1).

Results

Forty samples of semen were treated by this technique. After separation, large numbers of dead, non-motile and agglutinated sperm could be seen to lie at the interface between albumen and semen, along with many epithelial and polymorphonuclear cells. Down in the albumen column the sperm could be seen to be highly motile and free from seminal debris (Fig. 2). In all instances there was a considerable improvement in motility (from a mean of 45 to 74%, $P<0.001$) with elimination of autoagglutination. This was achieved, however, at the expense of a decrease in sperm density from a mean of 28.2×10^6 to 9.7×10^6 per ml ($P<0.001$) (Table 2).

Thirty-five intracervical and 5 intrauterine inseminations were performed in 18 women. There have been 3 pregnancies (16.7%) from intracervical insemination in each instance. The first pregnancy occurred from an initial sperm density of 30×10^6 per ml but motility of only 20% from which, after separation, 6×10^6 per ml with 60% motility were inseminated. The second occurred from semen with 5×10^6 per ml initial density with 50% motility, from which 0.25×10^6 per ml with 80% motility were inseminated. The third pregnancy happened with semen of good quality (90×10^6 per ml, 60% motility) but with marked autoagglutination. Separation yielded 30×10^6 per ml and 90% motility with marked reduction of autoagglutination (Table 3).

Table 2 Mean Change in Sperm Density and Motility after Separation

Mean	*Before*	*After*
Sperm density × 10^6 per ml	28.2	9.7
Motility %	45.4	74.3

Table 3 Sperm Profile in the 3 Pregnancies

	Sperm density × 10^6/ml *Before sepn.*	 *After sepn.*	*Motility %* *Before sepn.*	 *After sepn.*
Couple A	30 ●	6	20	60
Couple B	5	0.25	50	80
Couple C	90 ●	30	60	90

● = marked agglutination.

There has been one healthy girl born to date. The other 2 wives are in the third trimester of uncomplicated pregnancies. No serious complications were encountered with the inseminations. One woman had right-sided abdominal pain and cramps which resolved a few days after intrauterine insemination.

Perhaps it is important to point out that during the period of this pilot study a fourth patient also became pregnant, but this was during a cycle when AIH was suspended because the husband was ill.

Discussion

This technique is simple and needs no special equipment. It offers the advantage that only vigorously motile sperm are inseminated, while autoagglutinated, dead, and non-motile sperm are left behind together with any other debris, pus cells, and whatever factors there may be in the seminal plasma which might inhibit the sperm.

Although some workers in the past have found that oligozoospermic semen gives very disappointing results in AIH using conventional techniques (Dixon *et al.*, 1976; Speichinger and Mattox, 1976), in previous work from this department, using AIH, Usherwood (1978) reported a 28.1% pregnancy

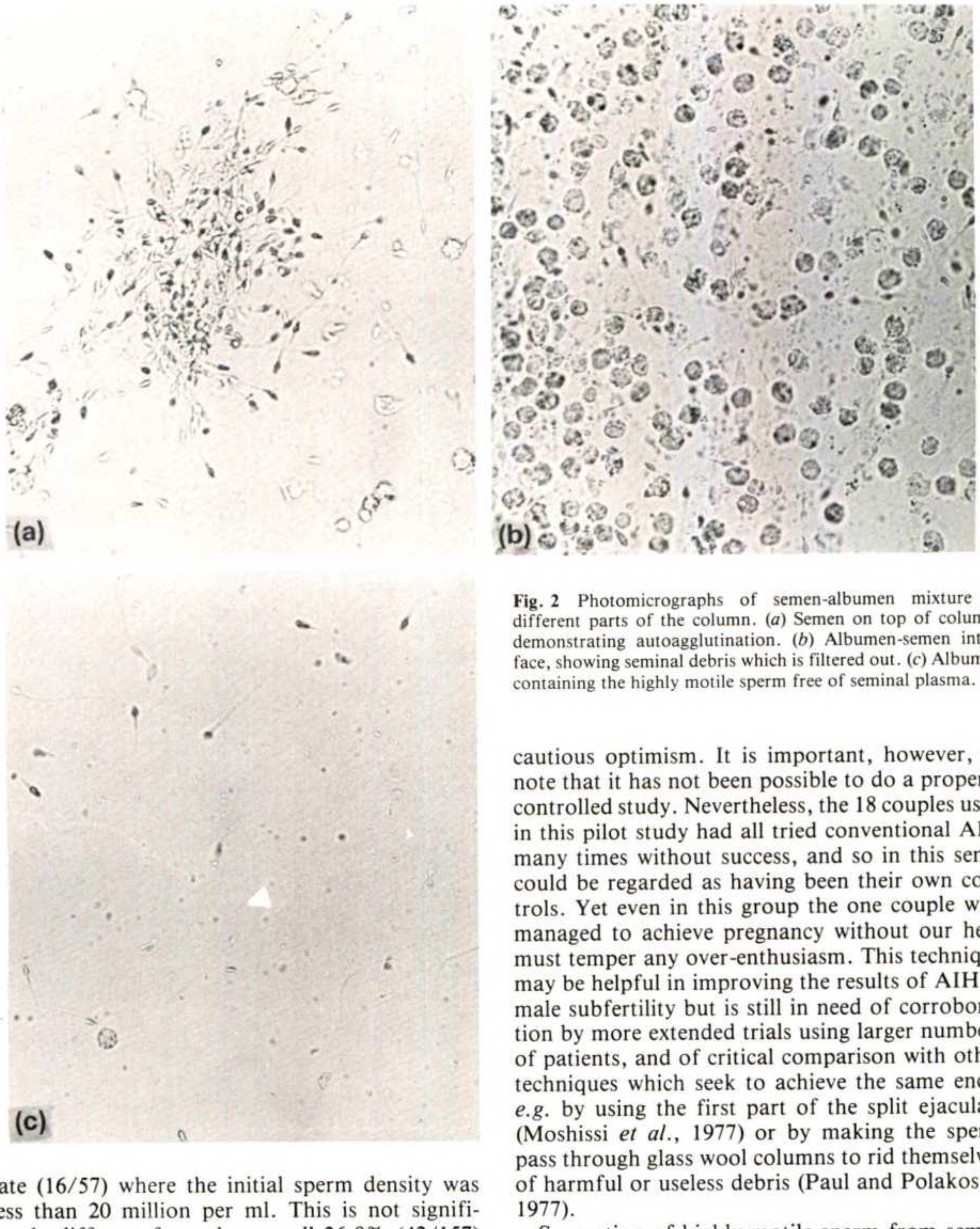

Fig. 2 Photomicrographs of semen-albumen mixture in different parts of the column. (*a*) Semen on top of column, demonstrating autoagglutination. (*b*) Albumen-semen interface, showing seminal debris which is filtered out. (*c*) Albumen containing the highly motile sperm free of seminal plasma.

rate (16/57) where the initial sperm density was less than 20 million per ml. This is not significantly different from the overall 26.8% (42/157) pregnancy rate or the success achieved in cases where sperm density was greater than 50 million per ml (12/53 = 22.6%).

These preliminary results give the basis for cautious optimism. It is important, however, to note that it has not been possible to do a properly controlled study. Nevertheless, the 18 couples used in this pilot study had all tried conventional AIH many times without success, and so in this sense could be regarded as having been their own controls. Yet even in this group the one couple who managed to achieve pregnancy without our help must temper any over-enthusiasm. This technique may be helpful in improving the results of AIH in male subfertility but is still in need of corroboration by more extended trials using larger numbers of patients, and of critical comparison with other techniques which seek to achieve the same ends, *e.g.* by using the first part of the split ejaculate (Moshissi *et al.*, 1977) or by making the sperm pass through glass wool columns to rid themselves of harmful or useless debris (Paul and Polakoski, 1977).

Separation of highly motile sperm from semen using an albumen column is a simple addition to our armamentarium. The 16.7% pregnancy rate in a small group of patients with prolonged infertility justifies further trial of this technique.

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Improvement of Semen and Pregnancy Rate after Ligation and Division of the Internal Spermatic Vein: Fact or Fiction?

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Summary—Male partners with left-sided varicoceles of 96 infertile couples were studied. Fifty-one patients were submitted to ligation of the testicular veins and 45 individuals were randomised as controls. During an observation period of 53 months (range 36 to 74 months) we found no statistically significant improvement in the semen crude variables, the morphology or the progressive motility in the series of men submitted to surgery. The pregnancy rate was lower in those who had an excision of varicocele.

Varicocele has been implicated as a common cause of male infertility (Dubin and Amelar, 1971) mainly on the basis of 3 observations:

1. The incidence of varicocele has been noted to be higher in the male partners of infertile couples than that in the general population (Russel, 1954; Dubin and Amelar, 1971).
2. The presence of varicocele is in some males associated with abnormalities in semen analysis (MacLeod, 1965; Schirren and Klosterhalfen, 1966) and testicular histology (Ibraham *et al.*, 1977; Johnsen and Agger, 1978).
3. Varicocelectomy has been noted to result in improvement in semen quality (Johnsen and Agger, 1978) and pregnancy rates (Dubin and Amelar, 1970; Brown, 1976).

However, the incidence of varicocele in the general population has been reported to be as high as 22.6% (Uehling, 1968) but is probably 10 to 15% (Clarke, 1966). Many patients with varicocele have normal fertility. The high incidence of varicocele in infertile male partners probably represents the fact that patients with a known varicocele are frequently referred to urologists with a particular interest in male infertility problems.

Nilsson *et al.* (1976) reported that varicocelectomy in a group of male patients did not improve mean sperm count, morphology or motility. In this series all cases of varicocelectomy with a subsequent pregnancy had a normal cervical mucus invasion test before and after operation. Herein we present our study to evaluate in a randomised series the relationship of varicocele to semen quality and fertility and to the effect of varicocelectomy.

Patients

Ninety-six couples fulfilling certain criteria (see below) were seen consecutively in our office for evaluation of infertility.

Diagnostic Evaluation

The patients had not been treated by other physicians before their referral. The method of evaluation was the same as that described earlier (Nilsson *et al.*, 1976). In brief, both members of the couple were managed by the same group of physicians. During the initial visit a complete history was obtained from both partners and a physical examination was performed on each.

The diagnosis of varicocele was established by examination of the patient in the upright position at room temperature (+22°C). In all subjects the varicose veins were visible and seen on the left side of the scrotum. None were bilateral. Reflux of blood into the pampiniform plexus was determined by manual palpation during a Valsalva manoeuvre.

The 96 men (patients and controls) were selected

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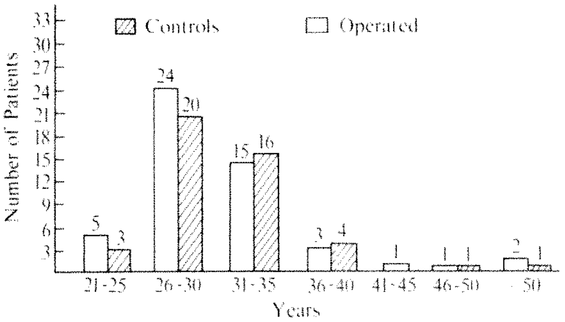

Fig. Age distribution of patients with varicocele.

from 165 individuals with varicocele attending the infertility clinic, with the aim of eliminating factors known to disturb spermatogenesis, *e.g.* previous operation for hydrocele of the testis or inguinal hernia during childhood, mumps orchitis contracted during or after puberty, unilateral or bilateral testicular retention corrected or not corrected by operation. Azoospermic men as well as patients autoimmunised to spermatozoa and those with raised follicle stimulating hormone were excluded; these changes are nearly always associated with severe and usually irreversible disorders of spermatogenesis.

The distribution of the male subjects within age groups is given in the Figure. The mean age of the 51 patients was 31 years (range 22-51 years) and of the 45 control subjects 30 years (range 21-52 years).

In the female partners the occurrence and adequacy of ovulation were evaluated during a minimum of 4 consecutive menstrual cycles. Emphasis was placed on basal body temperatures and on the observation of a cervical mucus of ovulatory character fulfilling the following criteria: clear without clumps or turbid areas, low viscosity, a "Spinnbarkeit" of at least 50 mm and a strongly positive fern test. Hormonal determinations, endometrial biopsies and laparoscopy were done if necessary. Bilateral tubal occlusion was not diagnosed in any female partner of men entering the study.

Medical therapy was not given to the husband. In no case was artificial insemination by the husband used.

All couples had sterile marriages and had tried to conceive for at least 2 years, in some instances for as long as 8 years. None of the husbands had offspring either earlier in their marriage or during a previous marriage.

Before entering the study all men had at least 3 seminal specimens analysed, spaced 3 to 5 weeks apart. During the follow-up fresh ejaculates were checked at an interval of 3 to 6 months.

Each specimen was examined as shown in Table 1. Sperm motility, percentage of living sperms and *in vitro* sperm penetration ability were examined within 2 h of collection.

The sperm penetration test was performed by means of the capillary tube technique devised by Kremer (1965) modified according to Nilsson *et al.* (1978). A penetration extent of more than 5.5 μm/s indicated a high probability of fertilising capacity, 5.2-1.6 μm/s reduced capacity and less than 1.5 μm/s probable lack of fertilising capacity. Only spermatozoa with a smooth and regular shape were recorded as "tapering". All irregular forms were classified as "amorphous". All of the semen analyses were performed in the same laboratory under the direction of one experienced observer.

Operative correction was performed by means of a modification of the supra-inguinal approach according to Palomo (1949), which permitted ligation not only of the internal spermatic vein(s) but also of the cremasteric vein in subjects with secondary varicosity of that system. No sign of varicocele was found at examination 6 months after the operation and at the follow-up the left testicle was neither atrophic nor in a higher position than normal.

Results

Ejaculate Volume

There was no significant difference between the values obtained before and after the operation (Table 2) and no difference between the patient and the control series.

Sperm Count and Total Sperm Count

Pre-operatively 60% of men with varicocele had sperm counts less than 40 million/ml and 26% had less than 20 million/ml. Table 2 shows that no significant change in sperm count and total sperm count could be determined after varicocelectomy and between the patient and control series. This observation was valid both when pre-operative sperm counts were less than or greater than 20 million/ml. Before operation 51 men (78%) had an average total sperm count less than 300 million/ejaculate. No specimen with polyzoospermia (>1000 million) was found. In 66%

Table 1 Methods for Sperm Analysis

Observation			*Methods*
Volume, ml			Calibrated tube
Number of spermatozoa, millions/l			Bürker chamber
Living spermatozoa (%)			Eosin staining
Motile (%) Motility degree (1-4) Agglutination, degree and type			Microscopic examination of a drop of fresh ejaculate
Abnormal forms	Amorphous	Heads	Staining acc. to Moench (>50% = abnormal)
	Small		
	Big		
	Tapering		
	Double		
	Abnormal mid-piece		
Leucocytes Erythrocytes Macrophages Epithelial cells Bacteria			Modified Giemsa staining
Acid phosphatases			Acc. to Sigma Technical Bulletin 104
Fructose			Acc. to Roe
Sperm agglutinating antibodies, serum Sperm agglutinating antibodies, seminal plasma			Gelatine agglutination test (Kibrick)
Sperm penetration			Kremer, modified by Nilsson *et al.*

of the patients there were considerable variations in the total number of sperms between samples delivered of the same individual on different occasions, while 34% of the subjects showed a variation between the samples which was less than 20%. After operation the total sperm count increased in 2 or more consecutive samples in 9 men (18%), decreased in 16 (31%) and was unchanged in 26 (51%).

Motility and Motile Sperm Count

No significant change in motility and motile sperm count could be demonstrated after varicocelectomy when pre-operative sperm counts were less than 10 million/ml. A slight but statistically insignificant increase in sperm motility was observed in the group of patients with preoperative sperm counts greater than 40 million/ml. There was no difference between the treated patients and controls.

Morphology

Before the operation 40 men (78%) had more than 50% abnormal forms. Thirty-eight (75%) had tapering forms, the percentage varying between 1 and 7% of the total number of spermatozoa. After operation the percentage of abnormal forms decreased more than 10 units in 2 or more consecutive samples in 10 patients (20%) and increased in 9 patients (18%). All 38 males who had tapering forms before varicocelectomy had those forms also after the operation, although the percentage was reduced by more than 3 units in 5 patients during the follow-up period.

In vitro *Sperm Penetration Ability*

The ability of sperm *in vitro* to penetrate the fraction of the white of a hen's egg that can replace cervical mucus (Nilsson *et al.*, 1978) in the Kremer test is shown in Table 3. Before varicocelectomy an average penetration extent of

Table 2 Semen Quality in Controls (45 Individuals) and 51 Patients with Varicocele Before and After Varicocelectomy

	Volume (ml)	*Sperm count (10^6/ml)*	*Total sperm count (10^6)*	*Motile (%)*	*Morphology (%)*	
					Tapering	*Amorph.*
Before	3.7 ± 1.7	47 ± 41	158 ± 121	32 ± 8	2 ± 2	56 ± 19
After	3.6 ± 1.8	49 ± 40	156 ± 133	32 ± 7	2 ± 2	56 ± 13
Controls	3.6 ± 1.7	54 ± 43	178 ± 143	31 ± 7	2 ± 2	57 ± 15

Table 3 Capillary Penetration Ability of Sperm Before and After Varicocelectomy —/, and in Controls /— (Pregnancy = P)

Pre-op (μm/s)				
>5·5				PP8/6 PPPP
3·9-5·5		1/	PP20/17 PPP	1/
1·7-3·6		11/14 P	2/	
<1·7	6/8	1/	1/	
	<1·7	1·7-3·6	3·9-5·5	>5·5

Post-op. (μm/s)

more than 5.5 μm/s, indicating a high probability of impregnating capacity, was found in the samples from 8 males; a slightly reduced penetrating ability (5.5-3.9 μm/s) was present in the samples from 22 individuals and a severely reduced penetration ability (3.6-1.7 μm/s) was found in the samples of 13 males. Lack of penetration (less than 1.7 μm/s) was found in the specimens of 8 males.

After surgery the average sperm penetration ability increased in 5 patients. Two subjects had an increase from below 1.7 μm/s. The sperm penetration ability was unchanged in 45 patients (90%) and was reduced in one subject.

Conception

During the follow-up period of 36 to 74 months (mean 53 months) the incidence of pregnancy in the 96 couples was 15% (12 couples, 14 pregnancies). The length of time required for pregnancy to occur ranged from one to 49 months. All males who impregnated their wives had a sperm penetration ability of more than 2.7 μm/s. They were not different in any other way from the other patients.

Four conceptions occurred among those subjected to varicocelectomy and 8 wives of men not operated upon conceived. None of the men whose spermatozoa showed an increase in penetration ability after varicocelectomy succeeded in impregnating their wives during the follow-up of 36 to 62 months.

Discussion

Treatment of infertile men with oligoteratozoospermia and/or reduced sperm motility provides little satisfaction except in cases where the disorder is combined with the presence of varicocele. In such cases an improvement of sperm quality can be expected in 60 to 70% of patients operated upon (MacLeod, 1965; Dubin and Amelar, 1975; Brown, 1976), and conception rates of 40 to 50% have been reported (MacLeod, 1969; Dubin and Amelar, 1975; Brown, 1976). The improvement in sperm quality is primarily due to improved sperm motility and to a lesser degree to an increased number of normal spermatozoa and raised sperm count (MacLeod, 1965; Dubin and Amelar, 1975).

Although it is generally accepted that varicocele can influence spermatogenesis and that ligation of the left testicular vein has a beneficial effect, the mechanism of action is still a tantalising problem. The most puzzling phenomenon is that although the varicocele is almost entirely on the left, the spermatogenic reduction is absolutely identical in both right and left testis (Agger and Johnsen, 1978). Furthermore, the duration of varicocele has no effect on spermatogenesis (Johnsen and Agger, 1978), nor has it been possible to correlate the size of the varicocele with the reduction of spermatogenesis (Agger and Johnsen, 1978). Many patients with varicocele have normal fertility.

The percentage of patients with varicocele attending our fertility clinic was 16%, a figure slightly higher but comparable to the incidence of varicocele in adult men. The incidence in the general population has been studied by a few investigators, who used somewhat different diagnostic criteria. An incidence of 10 to 15% has been reported (Clarke, 1966). Since approximately 15% of the general male population is thought to have some degree of varicocele it is not surprising that varicocele in some patients will be associated with reduced semen quality. MacLeod (1969) estimated that 40 to 50% of varicocele patients with infertile marriages had normal semen quality. The incidence of males with varicocele in the present series of males of infertile couples is remarkably low compared to other series (Cockett *et al.*, 1979). It probably reflects the fact that in the Göteborg region all infertile couples are referred to one clinic for investigation. The higher frequency (30-40%) in other series probably indicates that patients with a known varicocele frequently seek urologists with a particular interest in male reproductive surgery.

Since pregnancy relates to the fertility potential of both members of the couple, we aimed in this study to eliminate all couples where the female partner had bilateral tubal occlusions, severe ovulatory disturbances or defective cervical mucus. We also aimed to eliminate male subjects with disorders known to effect spermatogenesis, *e.g.* sperm antibodies, raised follicle stimulating hormone testicular retention azoospermia and spermatogenic arrest.

Reduction of semen quality was apparent in approximately 60% of the men with varicocele, a percentage similar to that reported by Hotchkiss (1944) and Cockett *et al.* (1979). Greenberg (1977), however, reported that more than 80% of men with varicocele had abnormal semen quality.

The evaluation of semen quality from one or more of the crude variables such as sperm count or sperm morphology is very often "a case of beauty being in the eye of the beholder" (Yeates, 1978) and their significance much overrated. We have found that the mucus invasion test of Kremer (1965), modified according to Nilsson *et al.* (1978) provides the closest correlation with proved fertility. In the present controlled series of men with varicocele we found no beneficial effect of varicocele ligation upon the crude variables, morphology or sperm motility. We were not able to demonstrate an increased pregnancy rate after surgery. Pregnancies occurred in this series in wives of men who had a normal mucus invasion test before as well as after operation. Men with varicocele and sperm of low penetrating capacity did not impregnate their wives irrespective of ligation of the testicular vein or not.

The present findings also suggest that although the presence of a varicocele is associated with compromised semen quality in some men, it is not necessarily associated with diminished fertility.

In the present series we had no failure rate for varicocele ligation, defining failure in terms of recurrent or residually dilated scrotal veins. At the present time it must be assumed that a man who has a good anatomical result but no improvement in semen quality after varicocele ligation has either suffered irreversible damage from the varicocele or has another cause for his subfertility.

The findings in this study are provocative and might show that the high incidence of varicocele in infertile men merely represents the end result of a diligent physical examination. It also indicates that varicoceles do not always cause infertility but perhaps merely are associated with it.

Success in the treatment of male infertility is often used to mean just an improvement in one or more of the crude variables originally found to be below acceptable values, though none of these may be the critical deficiency. The only true criterion of success is surely a pregnancy, but here there must always be suspicion of its occurrence being unrelated to treatment (Yeates, 1978).

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Negative Pressures in Surgical Drains

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Summary—Laboratory and clinical experiments were done to measure the pressure in tube drains. It was found that the fluid in drains connected to floor bags exerted a negative pressure equal to the height of the fluid column in the tube. There was no negative pressure when the drain opened into a urostomy bag at wound level. It is suggested that this negative pressure might tend to maintain a urinary fistula once a leak in the suture line has begun.

In considering the most suitable type of wound drain, the urologist is faced with a number of conflicting requirements: convenience for the patient, convenience for the nursing staff, risk of infection, ease of fixation and removal, and ability to cope with the anticipated type and volume of drainage.

Following renal surgery, for example nephrolithotomy or pyeloplasty, it is convenient to use a tube drain connected to a collecting bag that stands on the floor beside the bed. This arrangement, being closed, is theoretically less liable to infection. It is a convenient method for collecting any urine that may drain (Fig. 1).

After recently adopting this system we have had 3 unexpected and persistent urinary fistulae. This prompted an investigation of the hydrodynamics of these drains.

Materials and Methods

Laboratory Experiments

An apparatus was set up as shown in Figure 2. The motorised syringe represented the kidney, and the tubing the drainage system which was completely filled with water. A differential transducer connected to a Siemans Mimograf 82 was used to measure the pressures. The transducer was connected by a water filled line to the upper end of the drainage tube which was at the same level. Pressures were measured with the lower end of the tube at various levels below the bench top. The motorised syringe was set to deliver various flow rates up to 10 ml per min to simulate urine production by the kidney, and further measurements were made.

Clinical Observations

Nephrostomy Tubes Measurements were made on 5 patients who had 24 FG nephrostomy tubes inserted for the temporary drainage of kidneys

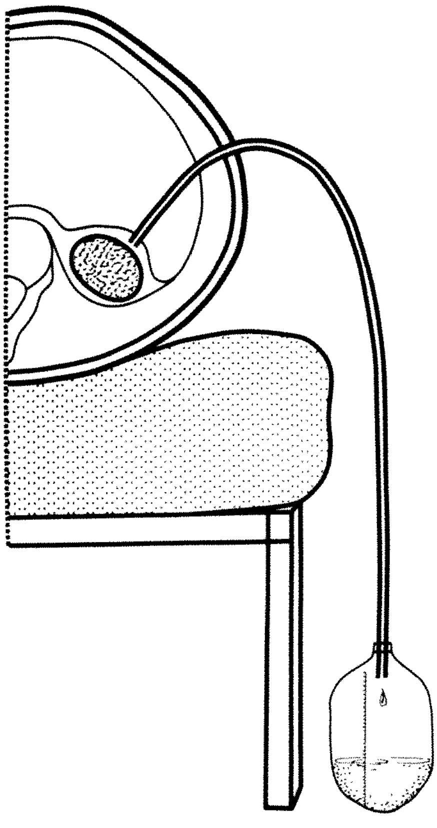

Fig. 1 Diagram showing the transverse section of a patient with a tube draining the kidney and connected to a floor bag.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

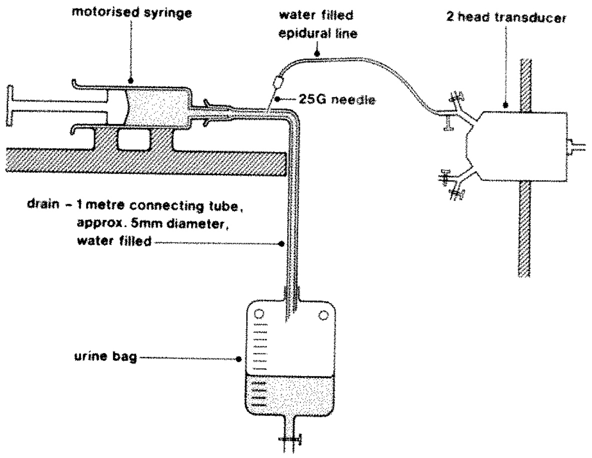
motorised syringe
water filled epidural line
2 head transducer
25G needle
drain - 1 metre connecting tube, approx. 5mm diameter, water filled
urine bag

Fig. 2 Diagram of laboratory apparatus used as a model for a tube drainage system.

after surgery. The drains were connected by a 1-metre tube to a urinary collecting bag (Aldon). For the purposes of measurement air bubbles were eliminated from the system. The transducer was set at the level of the renal pelvis with the patient supine and the pressures were measured as described.

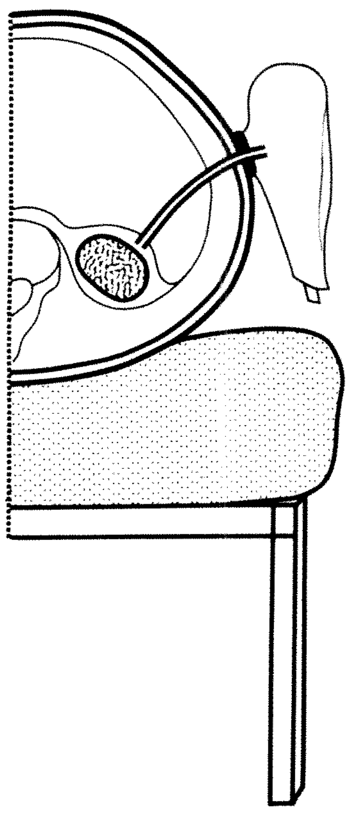

Fig. 3 Tube drain opening into a urostomy bag at wound level.

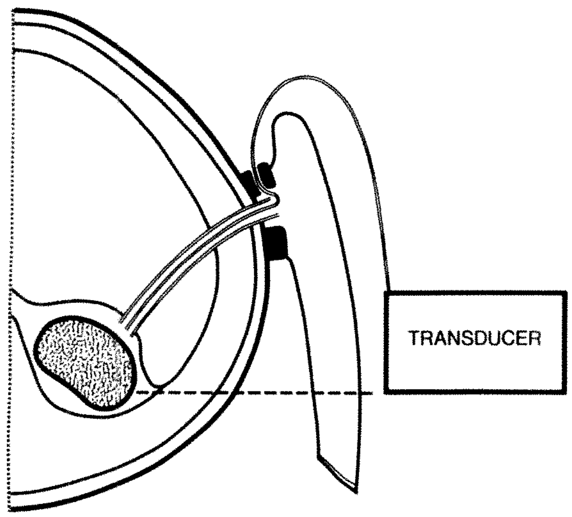

Fig. 4 Detail to show how the epidural line was passed through the Karaya gum ring of a urostomy bag.

Wound Drains In a further group of 12, observations were made on tubes used as wound drains in patients undergoing nephrolithotomy, pyelolithotomy and pyeloplasty. In each case a 24 FG tube was put down to the renal suture line in the renal fossa. The outer end of the tube was connected in one of 2 ways:

1. Attached to a floor drainage bag by a connecting tube (Fig. 1).
2. Left open into a urostomy bag at wound level (Fig. 3).

The pressure in the drain was measured in each case with a water-filled line and the transducer set at the level of the renal suture line. When a urostomy bag was used, the line was threaded through the Karaya gum sealing ring; the inner end of the line was passed down the drainage tube (Fig. 4).

In a further 2 patients with a urostomy bag the pressure in the drain was measured before and after connection to a floor drainage bag (Fig. 5).

Results

Laboratory Experiments

In each experiment there was a negative pressure at the upper end of the drain equal to the length in centimetres of the column of water below the

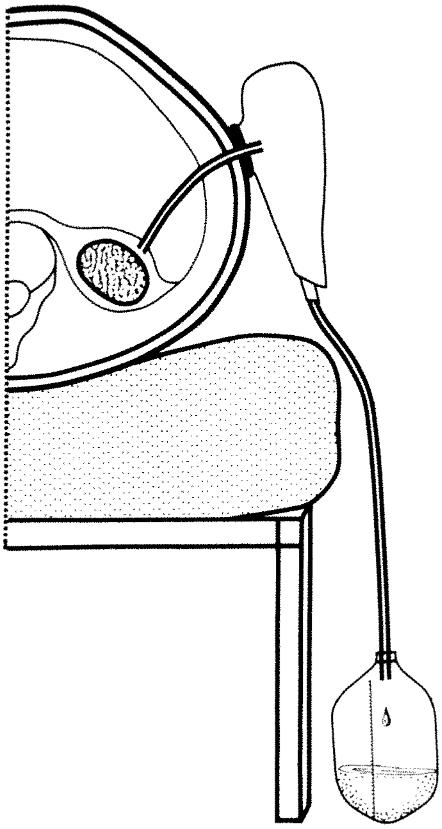

Fig. 5 Drain opening into a urostomy bag which was itself connected to a floor bag.

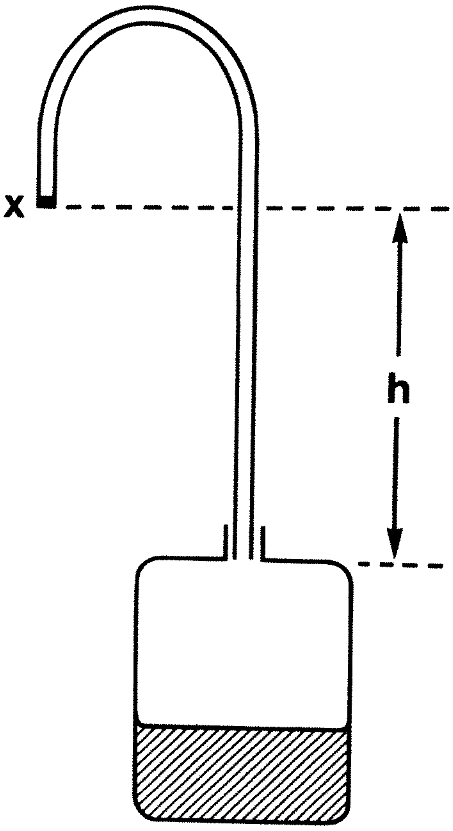

Fig. 6 The negative pressure exerted by a fluid-filled tube at point X is equal to the height h in centimetres of water.

bench top (Fig. 6). The pressure was independent of the flow rate up to 10 ml per min.

Clinical Observations

In these experiments the findings of the laboratory experiment were confirmed. If the nephrostomy tube was full of urine and connected directly to a collecting bag, a negative pressure was recorded equal to the height of the urine column in centimetres. In practice the negative pressure was between 25 and 30 cm of water when the collecting bag was hung from the bed frame and 50 to 55 cm when it was hung on a floor stand.

In the wound drains a pressure could only be measured if there was sufficient drainage to fill the tubing. In some cases there was not enough urine to eliminate all of the air bubbles and the readings are difficult to interpret. The results are shown in the table. With the drains connected to floor bags only 3 cases had a reasonable column of water and in all there was a negative pressure: it was nearly equal to the column height in 2 and in one it was only—16 cm with a column height of 30 cm. In case 2 the column height was 6.5 cm and the pressure +10 cm and in case 1 an empty tube appeared to exert a pressure of −16 cm: these results presumably reflect technical errors in measurement.

When the drain opened into a urostomy bag there was a small positive pressure in 4 and a negative pressure in one. When the urostomy bag was connected to a floor drainage bag there was a drop in pressure in the drain but it was not very great: from 0 to −3 cm in one and from +15 to 3 cm in the other.

The effect that the negative pressure in a drain might have is illustrated by case 4. After an uncomplicated pyelolithotomy the kidney was drained by a tube connected to a floor bag. A leak developed and drained between 700 and 1300 ml for 7 days. When the tube was removed the fistula remained open for a further 3 days.

Table Pressure Measurements in Tube Drains

	Case No.	*Height of Column* (cm)	*Pressure* (cm)
Tube drain with floor bag	1	0	−16
	2	6.5	+10
	3	30	−16
	4	45	−40
	5	48	−45
	6	0	0
	7	0	0
Tube in urostomy bag	8	—	−4
	9	—	+6
	10	—	+2.5
	11	—	+3
	12	—	+3.5

Discussion

The principle of transferring water from one container to another at a lower level by a siphon tube is well known. The system works because a negative pressure relative to atmospheric pressure is generated at the upper end by the column of water in the tube. This negative contribution to the pressure is equal to the height of the column in centimetres. This investigation has shown that a fluid-filled tube drainage system exerts a negative pressure and so conforms to this well known physical principle. The negative pressure is not altered by the flow rate likely to be generated by the kidney.

In tube drains if there is no urine leak there is, of course, no negative pressure. However, once a leak has begun the tube fills up and the negative pressure may tend to keep the fistula open. There is no negative pressure when the tube opens directly into a urostomy bag.

No attention appears to have been paid to the existence of this hydrostatic pressure in the past. An increased morbidity with tube drains has been described (Golovsky and Conolly, 1976) but it was not recorded whether floor drainage bags were used for these patients. It may be that the negative "siphon" pressure was an important contributory factor.

It has been suggested that the mere presence of a drain leads to leakage in colonic anastomoses (Crowson and Wilson, 1973). However, there are situations, particularly in urological patients, when a drain of some kind must be used. If a small suction pressure is required suitable systems have been described (Blackwood, 1975; Garcia-Rinaldi *et al.*, 1975). When an anastomosis has been made that is expected to be watertight it does not seem logical to apply a negative pressure to the outside of it. The knowledge that a tube connected to a floor bag exerts a negative pressure when full of urine should deter the surgeon from using such a system. When a closed drainage system is essential, the anastomosis may be protected by allowing the tube drain to open into a urostomy bag at wound level. We are now investigating a series of patients to assess the extent of the risk that this negative pressure causes.

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Prizes and Awards

British Association of Urological Surgeons: Annual Meeting Bristol. 4-6 July 1979

At the conclusion of the Annual Meeting Professor J. P. Mitchell, President of the Association, announced the following prizes and awards:

1. BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £500 for the best article in each volume of the *British Journal of Urology*. Candidates for the prize must be Fellows of one of the Royal Colleges of Surgeons in the British Isles, Canada, Australasia, or South Africa; they must be undergoing urological training or have obtained consultant posts within 10 years of the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prize winner must submit a programme of visits to Urological Centres outside Britain for consideration by the Council.

The 1979 prize for the best article in Volume 50, 1978, was awarded to Mr H. N. Whitfield for his article entitled "The distinction between obstructive uropathy and nephropathy by radioisotope transit times", *British Journal of Urology* (1978), **50**, 433-436.

2. C. R. Bard Award

Presented by C. R. Bard International Limited, the prize consists of £250 (index linked) and a Silver Medal on which the winner's name is engraved. It is awarded annually to the author who, in the opinion of a panel of BAUS members, has presented the best paper at their Annual Meeting.

The first recipient was Mr D. G. Thomas, author of "The urological status of 86 females following spinal cord injury", read at the 1979 BAUS Annual Meeting.

3. Eschmann Prize

At the 1979 BAUS Annual Meeting in Bristol, Eschmann Brothers and Walsh Limited very kindly donated a prize of £150 for the best Scientific Exhibit and the prize was given to Mr A. V. Hirsh and Mr J. P. Pryor for their exhibit on "Haemodynamics of varicocele: the Doppler effect".

Conversion Table—S.I. units

Old units			*Conversion factor multiply by:*		*S.I. units*	
Constituent	*Normal range*	*Units*	*Old to new*	*New to old*	*Normal range*	*Units*
Venous blood						
Albumin	3.5-5.5	g/100 ml	10	0.1	35-55	g/l
Bicarbonate (total)	24-30	mEq/l	1	1	24-30	mmol/l
Bilirubin	0.1-0.8	mg/100 ml	17	0.059	2-14	μmol/l
Calcium	8.6-10.5	mg/100 ml	0.25	4	2.15-2.65	mmol/l
Chloride	100-107	mEq/l	1	1	100-107	mmol/l
Cholesterol	140-240	mg/100 ml	0.026	38.5	4.0-6.5	mmol/l
Creatinine	0.6-1.4	mg/100 ml	88	0.0114	55-125	μmol/l
Glucose	65-95	mg/100 ml	0.056	18	3.5-5.5	mmol/l
Iron	110-130	μg/100 ml	0.18	5.6	circa 20	μmol/l
Magnesium	1.4-1.8	mEq/l	0.5	2	0.70-0.90	mmol/l
Phosphate	2.5-4.5	mg/100 ml	0.32	3.1	0.8-1.4	mmol/l
Potassium	3.8-5.2	mEq/l	1	1	3.8-5.2	mmol/l
Protein (total)	6.5-8.0	g/100 ml	10	0.1	65-80	g/l
P.B.I.	3.75-7.5	μg/100 ml	79	0.0127	300-600	nmol/l
IgG	500-1600	mg/100 ml	0.01	100	5.0-16.0	g/l
IgA	125-425	mg/100 ml	0.01	100	1.25-4.25	g/l
IgM	50-180	mg/100 ml	0.01	100	0.5-1.8	g/l
Sodium	136-149	mEq/l	1	1	136-149	mmol/l
Transferrin	150-300	mg/100 ml	0.01	100	1.5-3.0	g/l
Triglyceride	60-140	mg/100 ml	0.0113	88.5	M2.0 P<1.5	mmol/l
Uric acid	2-7	mg/100 ml	0.06	16.7	0.1-0.4	mmol/l
Urea	15-40	mg/100 ml	0.17	6.0	2.5-6.5	mmol/l
Arterial blood						
Base excess	−3-+3	mEq/l	1	1	−3-+3	mmol/l
PCO_2	32-46	mmHg	0.135	7.5	4.5-6.0	kPa
PO_2	80-100	mmHg	0.133	7.5	10.5-13.5	kPa
Urine outputs/24 h						
Calcium	200	mg	0.025	40	5	mmol
Creatinine	1-2	g	8.8	0.113	9-18	mmol
5HIAA	3-17	mg	5.23	0.19	16-90	μmol
Inorganic P.	1000	mg	0.032	31	30	mmol
Magnesium	100	mg	0.041	24	4.2	mmol
Potassium	70	mEq	1	1	70	mmol
Protein	<0.05	g	1	1	<0.05	g
Sodium	200	mEq	1	1	200	mmol
Urea	25	g	17	0.06	400	mmol
Uric acid	500	mg	0.006	167	3.0	mmol
VMA	<7	mg	5.05	0.2	<35	μmol

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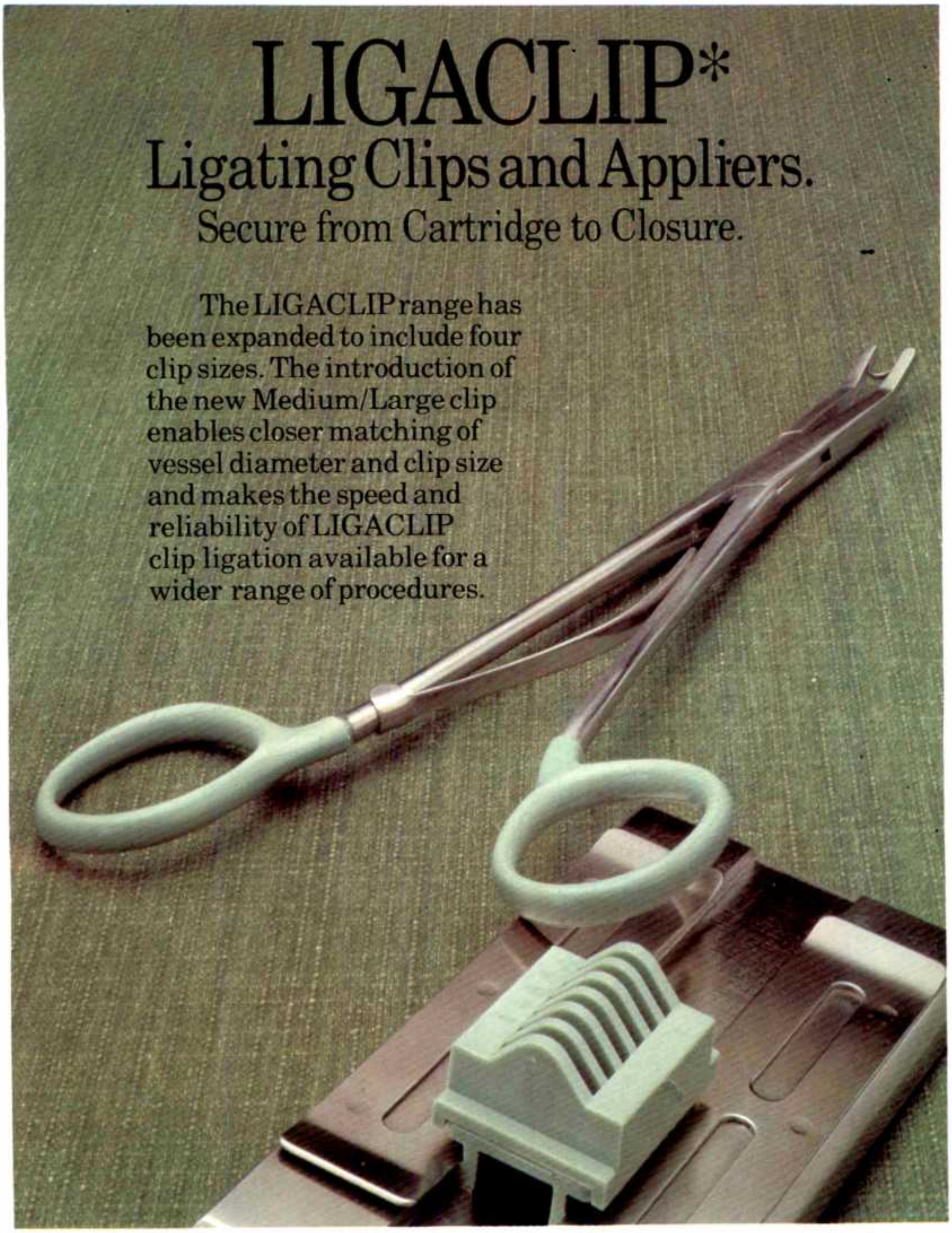

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